A STUDY ON PREVALENCE OF MICROALBUMINURIA IN HIV PATIENTS NOT ON ART AND CORRELATION WITH CD4 COUNT

submitted to

The Tamil Nadu Dr.M.G.R.Medical University

M.D. DEGREE EXAMINATION

BRANCH – I (GENERAL MEDICINE)

THE TAMIL NADU DR. M. G. R. MEDICAL UNIVERSITY

CHENNAI

MARCH 2009

BONAFIDE CERTIFICATE

This is to certify that **"A STUDY ON PREVALENCE OF MICROALBUMINURIA IN HIV PATIENTS NOT ON ART AND CORRELATION WITH CD4 COUNT "** is a bonafide work done by **Dr. MALIYAPPA VIJAY KUMAR**, post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of regulations of **The Tamilnadu Dr.M.G.R.Medical University** for the award of **M.D. Degree Branch I (General Medicine)** during the academic period from May 2006 to March 2009.

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KILPAUK, CHENNAI-10.
Venue: Dean Chamber, Date: 3.1.2008

Chair person
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TO WHOMSOEVER IT MAY CONCERN

Dear Sir / Madam

Sub: Internal Medicine – MD PG's Dissertation Ethical Committee – Reg.

Ref: Requisition from H.O.D. Medicine.

This is in reference to the letter dated 2.1.2008 regarding Ethical committee meeting clearance with regard to the following topics

Sl.No	Name of the Post Graduate	Dissertation Topic
1	Dr. R.Ramprasad	A study on Prevalence and Risk Factors of Diabetic Nephropathy in Newly Detected Type 2 Diabetic Patients
2	Dr. V.Sakthivadivel	A study on Cardiac abnormalities in HIV infected individuals
3	Dr. K.S.Gopakumar	A study on Subclinical Hypothyroidism in females over 50 years of age
4	Dr. T.Karthikeyan	Inflammatory profile in Acute Myocardial Infarction

5	Dr. Maliyappa Vijay Kumar	A study on Prevalence of Microalbuminuria in HIV patients not on ART and Correlation with CD4 count
6	Dr. D.Radha	High sensitivity C - reactive protein as a determinant in the outcome of Acute ischemic stroke
7	Dr. Lakshmi Thampy M.S	A Study on the prevalence of increased LV mass & Proteinuria in newly diagnosed Hypertensive patients.
8	Dr. Manu Bhasker	A study on the effect of Intravenous Metoprolol along with Thrombolysis in Acute Myocardial infarction
9	Dr. P.Mohanraj	Evaluation of Lipid Profile in patients with non diabetic Chronic Kidney Disease Stage 3,4 and 5
10	Dr. P.Dhanalakshmi	A study On Metabolic Syndrome in Young Ischemic Stroke
11	Dr. V.Murugesan	A study on Electrocardiographic and Echocardiographic changes in Chronic Obstructive Airway Disease
12	Dr. M.Seetha	Effect of Right ventricular infarction on the immediate prognosis of Inferior wall Myocardial Infarction

We are glad to inform you that at the EC meeting held on 3.1.08 on the above topics were discussed and **Ethically approved**.

DEAN

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We confirm that no member of the study team is on the Ethics Committee and no member of the study team voted.

The trial will also follow the Ethics Guidelines for Bio-Medical Research On Human subjects issued by ICMR, New Delhi and will not involve any expense to the Government and will not be detrimental to the normal functioning of the Institution.

The study will also satisfy the revised order issued by the Government of Tamil Nadu, Health and Family Welfare Department G.O.MS.No:319, H & FW, Dept. dated 30.11.2001.

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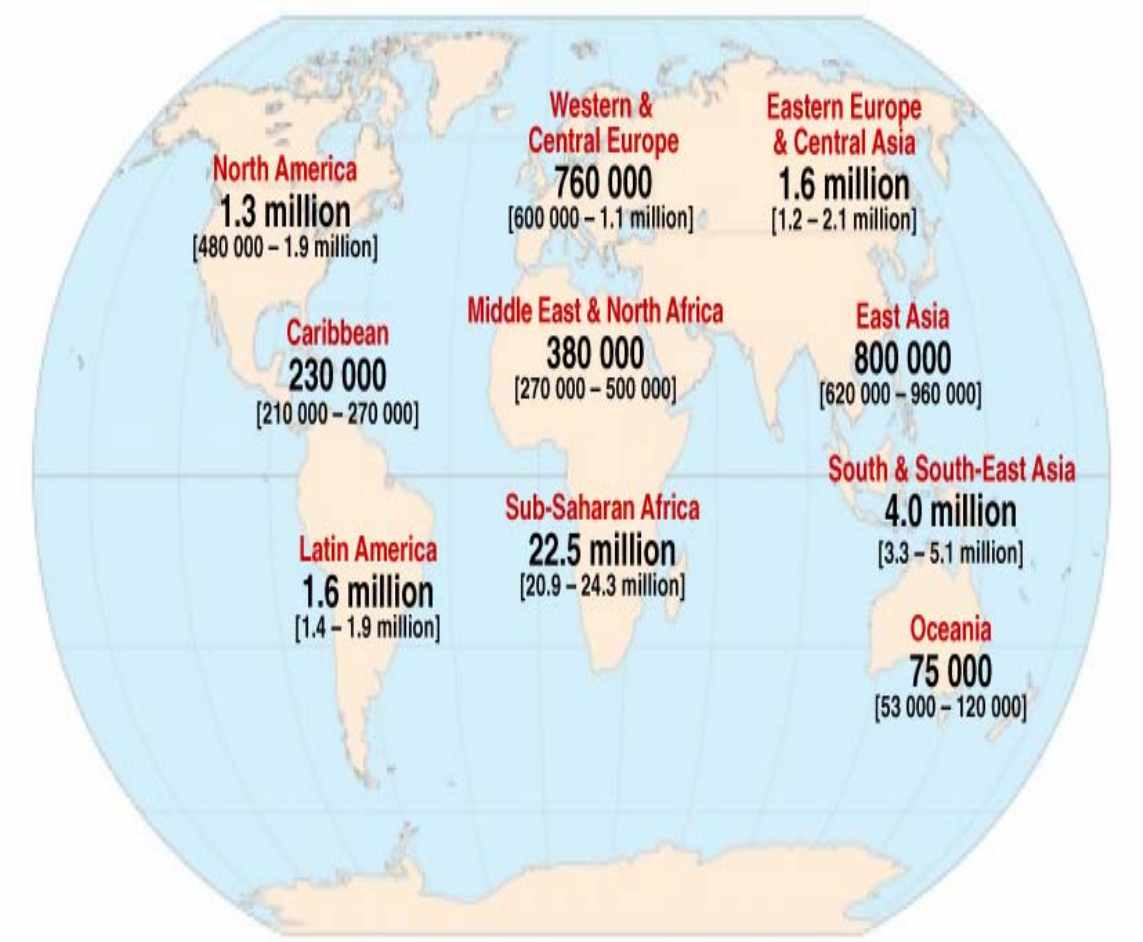
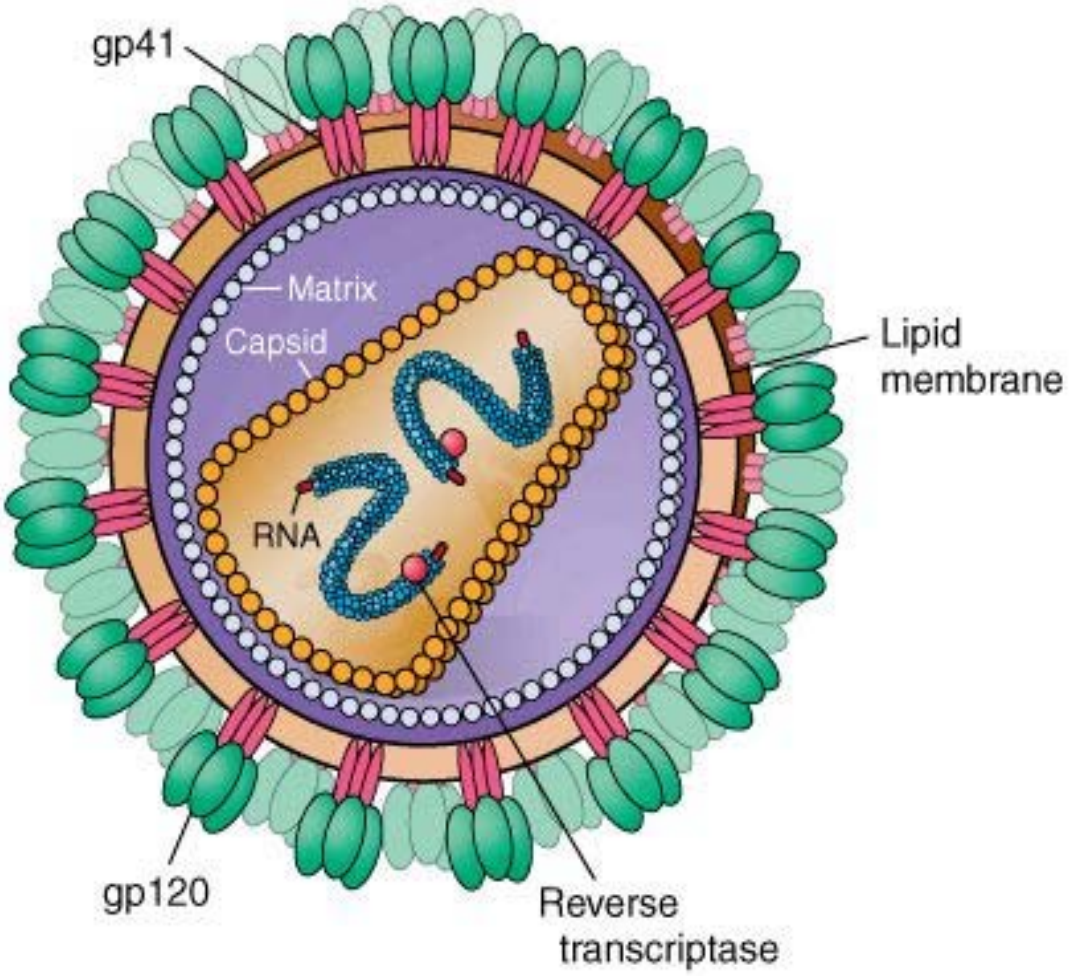
CONTENTS

Sl.No.	Title	Page No.
1.	INTRODUCTION	1
2.	AIMS OF THE STUDY	3
3.	REVIEW OF LITERATURE	4
4.	MATERIALS AND METHODS	42
5.	RESULTS	50
6.	DISCUSSION	64
7.	SUMMARY	70
8.	CONCLUSION	71
9	ANNEXURES	
	Charts	
	Master Chart	
	Proforma	
10.	ABBREVIATION	
11.	BIBLIOGRAPHY	

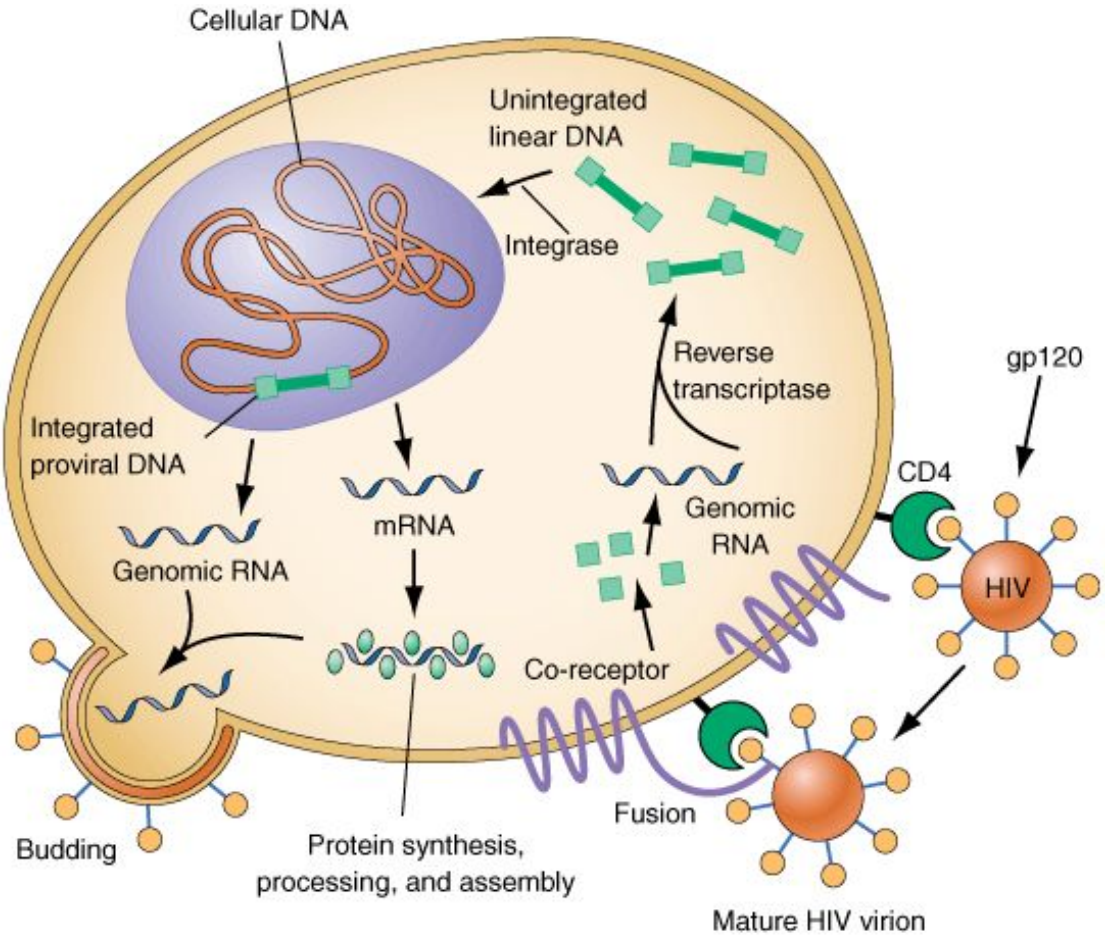
Global Estimates of HIV – 2007.
UNAIDS



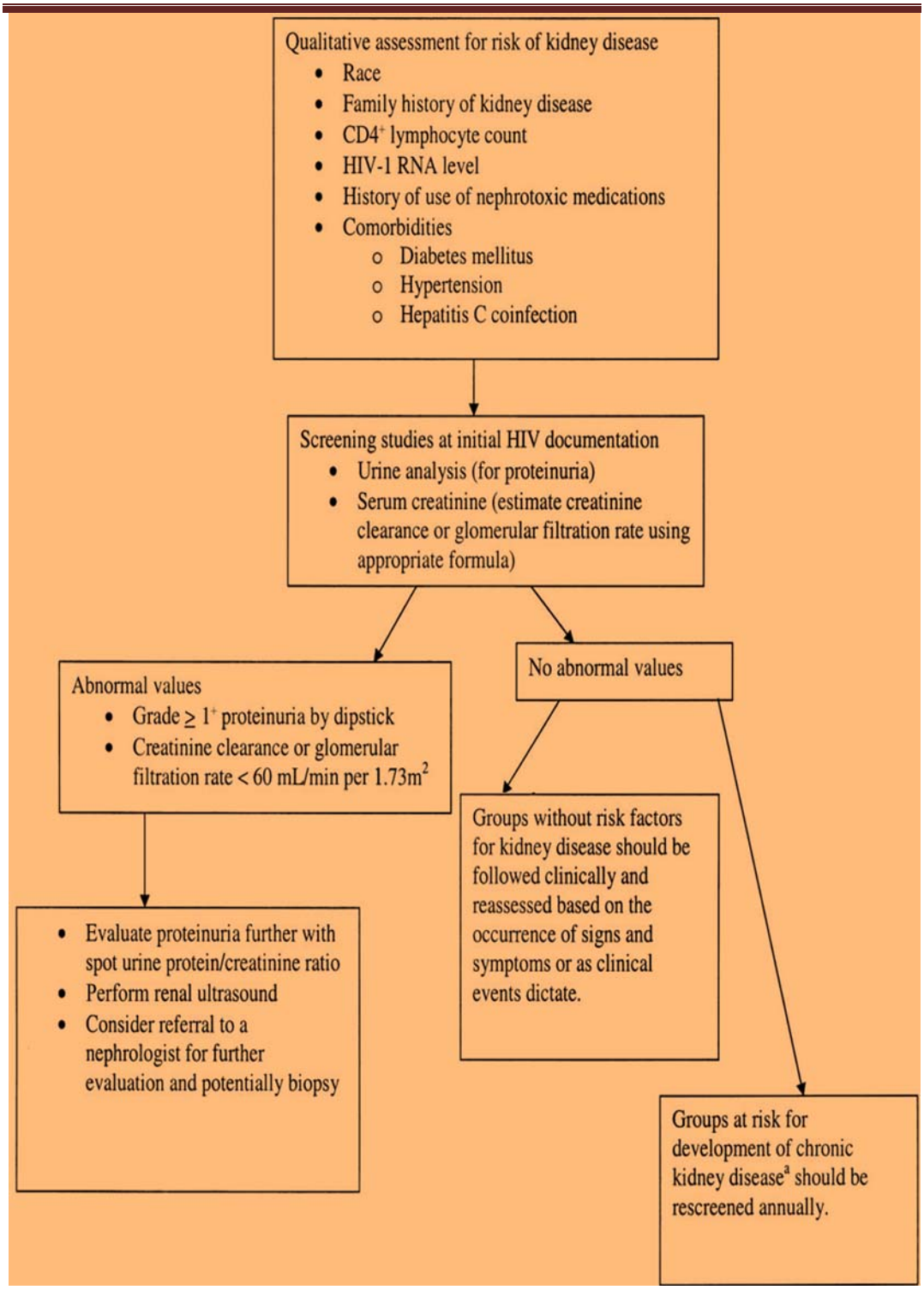
HIV GENOME


gp41
Matrix
Capsid
Lipid membrane
RNA
gp120
Reverse transcriptase

REPLICATION CYCLE OF HIV



Screening algorithm for HIV related Renal disease-Infectious Disease Society of America Guidelines



INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is spreading worldwide in pandemic proportions. It manifests from an asymptomatic state to AIDS. Involvement of multiple organs is well documented. Renal involvement occurs due to infection per se or due to associated problems like opportunistic/co-infections, septicaemia, drug toxicity[1,2]. Renal disease was first reported in HIV-1–seropositive individuals in 1984, and initial reports identified focal segmental glomerulo-sclerosis (FSGS) and other renal disease. Renal involvement is seen in all stages of infection presenting as fluid and electrolyte imbalance, HIV associated nephropathy (HIVAN) progressing to End Stage renal Disease (ESRD).

Survival of patients with HIV after HAART therapy has been introduced, has increased and so are the number of HIV cases with Chronic Kidney Disease (CKD)[3]. Cohort studies suggest that approximately 30% of HIV-positive individuals have proteinuria (≥ 1+)[4].

Microalbuminuria is an independent and earliest marker of renal involvement and loss of endothelial integrity. Overall microalbuminuria is seen in ~ 20% (varying from 9% to 30% in various studies) of untreated HIV infected patients[5,6,7,8,9,10]. Microalbuminuria levels showed correlation with CD4 T cell count suggesting an association

between the progression of disease and microalbuminuria[8,9]. Present study was undertaken to confirm or refute the earlier reports.

AIM & OBJECTIVES

1. To estimate the prevalence of microlalbuminuria in HIV patients

2. To correlate prevalence of microalbuminuria with CD4 cell count.

REVIEW OF LITERATURE

HUMAN IMMUNODEFICIENCY VIRUS[11]

The origin of HIV is unclear. In 1983 it was isolated from a patient with lymphadenopathy and in 1984 it was demonstrated clearly to be the causative agent of AIDS[11]. India's first case of AIDS was reported in 1986 from Chennai[12].

EPIDEMIOLOGY

GLOBAL SCENARIO[13]:

- An estimated 33 million people [30.3 – 36.1 million] were living with HIV in 2007.
- There were 2.7 million [2.2 – 3.2 million] new HIV infections and 2 million [1.8 – 2.3 million] AIDS-related deaths in 2007.
- Number of children younger than 15 years living with HIV 2.0 million (1.9-2.3 million) in 2007.
- An estimated 370 000 [330 000–410 000] children younger than 15 years became infected with HIV in 2007.
- The rate of new HIV infections has fallen in several countries barring Sub-Saharan Africa.
- Sub- Saharan Africa continues to dominate the statistics with 22.5 million of Adults and Children living with HIV.

- Globally, women account for half of all HIV infections—this percentage has remained stable for the past several years.
- The total number of children living with HIV has increased from 1.6 million [1.4 – 2.1 million] in 2001 to 2 million [1.9 – 2.3 million] in 2007 - almost 90% live in sub-Saharan Africa.

INDIAN SCENARIO[13,14]:

- Number of people living with HIV: 2 400 000.
- India ranks 3rd in total number of HIV patients in a country.
- Adults aged 15 to 49 prevalence rate: 0.3%.
- Adults aged 15 and up living with HIV: 2 300 000.
- Women aged 15 and up living with HIV: 880 000.
- Percentage of coverage of ART for prevention of mother to child transmission: <25%.
- Prevalence was higher in urban areas than in rural areas.
- Prevalence was higher among male than female in all age groups except those 15 to 19 years of age, in which rates were very low.
- HIV prevalence was stable or declining among pregnant women in the high prevalence states of Andhra Pradesh, Karnataka and Tamil Nadu.

- HIV transmission is primarily sexual, except in northeastern India where there is high rate of spread through injection-drug use.

SCENARIO IN TAMILNADU [15]

HIV prevalence in different population is as follows

- Antenatal clinic attendees – 0.25%.
- STD clinic attendees – 8%.
- Female sex workers – 4.62%.
- Men having sex with men – 5.60%.
- Intra venous drug abusers – 24.2%.

District Categorization [15]

- **Category A:** More than 1% ANC prevalence in district in any of the sites in the last 3 years.
- **Category B:** Less than 1% ANC prevalence in all the sites during last 3 years with more than 5% prevalence in any HRG site (STD/FSW/MSM/IDU).
- **Category C:** Less than 1% ANC prevalence in all sites during last 3 years with less than 5% in all HRG sites, with known hot spots (Migrants, truckers, large aggregation of factory workers, tourist etc).

- **Category D:** Less than 1% ANC prevalence in all sites during last 3 years with less than 5% in all HRG sites with no known hot spots and no or poor HIV data.

- In Tamil Nadu, among 30 districts, 22 districts are in category A, 5 districts are in category B and 3 districts are in category C.

ETIOLOGIC AGENT[11]

The etiologic agent of AIDS is Human Immunodeficiency Virus (HIV) which belongs to the family of human retroviruses (Retroviridae) and the sub family of lentiviruses. There are two subtypes of HIV namely HIV-1 and HIV-2. They are cytopathic viruses. HIV-1 was discovered by Luc Montagnier and his associates at the Institute of Pasteur in Paris in 1983. HIV-2 is more similar to SIV (Simian Immunodeficiency Virus) than HIV-1 and is much less virulent usually not resulting in full blown AIDS, but still fatal.

MORPHOLOGY OF HIV[11]

Electron microscopy shows that the HIV is spherical enveloped virus, about 90- 120 nm in size. The nucleocapsid has an outer icosahedral shell containing numerous external spikes formed by the two major envelope proteins, the external gp 120 and the transmembrane gp 41. The core virus particle is composed of ribonucleoproteins.

HIV GENOME[11]

HIV-1 has the following genes. Gag – encodes the proteins that form the core of virion. pol – encodes viral enzymes necessary for replication, reverse transcriptase, integrase and protease. env – encode glycoprotein. It also contains atleast six other genes tat, rev, nef, vpr, vpu which code for proteins involved in the regulation of gene expression.

The major difference between the genomes of HIV-1 and HIV-2 is the fact that HIV-2 lacks the vpu gene and has vpx gene not contained in HIV-1.

LIFE CYCLE[11]

ATTACHMENT AND ENTRY

The replication cycle of HIV begins with the high affinity binding of the gp 120 protein via a portion of its v1 region near the N terminus to its receptor on the host cell surface, the CD4 molecule. It is also expressed on the surface of monocytes and dentrites /langerhans cells. Once gp 120 binds to CD4, the gp 120 undergoes a conformational change that facilitates binding to one of a group of co-receptors. The two major co-receptors are CCR5 and CXCR4.

REVERSE TRANSCRIPTION AND INTEGRATION

Following binding of the envelope protein to the CD4 molecule, the virus is "uncoated" and the viral RNA is converted into complementary DNA (C-DNA) by virion associated reverse transcriptase enzyme. The C-DNA is transported to the host cell nucleus and eventually gets incorperated into the host cell chromosomes by virus specific integrase enzyme.

TRANSCRIPTION, TRANSLATION AND REPLICATION

The integrated DNA is transcribed into messenger RNA (mRNA) which comes out into cytoplasm and viral proteins are synthesized using protein synthesizing machinery and raw material from the host cell. Some of the viral proteins are synthesized as polyproteins that are eventually cleared by the proteinase enzyme.

MATURATION AND RELEASE

Newly synthesized progeny RNA and proteins are packaged together and the newly formed virus particles are released from the infected cell by the budding process.

PROGRESSION OF ILLNESS[11]

The median time from primary HIV infection to the development of

AIDS in untreated individuals is approximately 10 years. Individuals are considered to be long term survivors if they remain alive for ≥ 20 years after initial infection. It may be related to beneficial effect of ART and prophylaxis against opportunistic infections. Long term nonprogressors are those who have been infected with HIV for ≥ 10 years whose CD4 count are in the normal range and remained stable over years and who had not received ART.

The reasons being[11,16,17]

1. Mutant nef gene of HIV
2. Heterozygosity for CCR5- Δ32 deletion
3. Heterozygosity for CCR2-64I mutation
4. Homozygosity for SDF1-3'A mutation
5. Heterozygosity for the RANTES-28G mutation

CLASSIFICATION[11]

Table-1

CD4+ cell count(per microlitre) Categories	Clinical categories		
	A	**B**	**C**
	Asymptomatic, Acute (primary) HIV or PGL	Symptomatic, Not A or C Conditions	AIDS-Indicator Conditions
>500/µl	A1	B1	C1
200-499/µl	A2	B2	C2
<200/ µl	A3	B3	C3

PGL – Progressive Generalized Lymphadenopathy

HIV infected persons classified in A3, B3, C1, C2 and C3 are AIDS cases

Category A:

One or more of the following conditions in adolescents or adults (>13 years) with documented HIV infection.

Conditions listed in categories B and C must not have occurred.

1. Asymptomatic HIV infection
2. Progressive Generalized Lymphadenopathy

3. Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B:

Consists of symptomatic conditions in an HIV infected adolescent or adult that are not included among conditions listed in clinical category C and that meets one of the following criteria

1. The conditions are attributed to HIV infection or are indicative of a defect in cell mediated immunity (CMI).
2. Conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection.

Examples include, but are not limited to the following

a. Bacillary angiomatosis
b. Candidiasis, oropharyngeal (thrush)
c. Candidiasis, vulvovaginal: persistent, frequent or poorly responsive to therapy
d. Cervical dysplasia (moderate or severe)/ cervical carcinoma in situ
e. Constitutional symptoms, fever or diarrhea lasting >1 month
f. Oral hairy leukoplakia
g. Herpes zoster involving at least 2 distinct episodes or more than one dermatome.

h. Idiopathic thrombocytopenic purpura

i. Listeriosis

j. Pelvic inflammatory disease, particularly complicated by tubo ovarian abscess

k. Peripheral neuropathy

Categoty C:

Conditions listed in AIDS surveillance case definition

a. Candidiasis of bronchi, trachea or lungs

b. Candidiasis, esophageal

c. Cervical cancer, invasive

d. Coccidioidomycosis, disseminated or extrapulmonary

e. Cryptococcosis, extrapulmonary

f. Cryptosporidiosis, chronic intestinal (>1 month duration)

g. Cytomegalovirus disease (other than liver, spleen or nodes)

h. Cytomegalovirus retinitis (with loss of vision)

i. Encephalopathy, HIV related

j. Herpes simplex: chronic ulcers (>1 month duration) or bronchitis, pneumonia or esophagitis

k. Histoplasmosis, disseminated or extra pulmonary

l. Isosporiasis, chronic intestinal (>1 month duration)

m. Kaposi's sarcoma

n. Lymphoma, Burkitt's (or equivalent term)

o. Lymphoma, primary of brain

p. Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary

q. Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)

r. Mycobacterium, other species or unidentified species, disseminated or extrapulmonary

s. Pneumocystis jiroveci pneumonia

t. Pneumonia, recurrent

u. Progressive multifocal leukoencephalopathy

v. Salmonella septicemia, recurrent

w. Toxoplasmosis of brain

x. Wasting syndrome due to HIV

CLASSIFICATION OF HIV INFECTION (WHO CLINICAL STAGING SYSTEM)[18]

Clinical stage 1:

a. Asymptomatic

b. Persistent Generalized Lymphadenopathy

Clinical stage 2:

a. Weight loss <10% of body weight

b. Recurrent upper respiratory tract infections (e.g. bacterial sinusitis)

c. Herpes zoster

d. Angular cheilitis

e. Recurrent oral ulceration

f. Papular pruritic eruptions

g. Seborrhoeic dermatitis

h. Fungal nail infections

Clinical stage 3:

a. Weight loss > 10% of body weight

b. Unexplained chronic diarrhea > 1 month

c. Unexplained persistent fever (intermittent or constant) > 1 month

d. Persistent Oral Candidiasis (thrush)

e. Oral hairy leukoplakia

f. Pulmonary tuberculosis

g. Severe bacterial infections (e.g. pneumonia, pyomyositis)

h. Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

i. Unexplained anemia (< 8 g / dl), neutropenia (< 0.5 X 10^9 / litre) and or chronic thrombocytopenia

Clinical stage 4:

a. HIV wasting syndrome

b. Pneumocystis jiroveci pneumonia

c. Recurrent severe bacterial pneumonia

d. Toxoplasmosis of the brain

e. Chronic Cryptosporidiosis

f. Chronic Isosporiasis

g. Cryptococcosis - extrapulmonary

h. Cytomegalovirus infection (retinitis or infection of other organs)

i. HIV Encephalopathy

j. Chronic Herpes simplex infection (orolabial, genital or anorectal of > 1 month's duration or visceral at any site)

k. Disseminated endemic mycosis (Extrapulmonary Histoplasmosis, Coccidiomycosis)

l. Kaposi's sarcoma

m. Candidiasis - esophagus, trachea, bronchi or lungs

n. Disseminated non-tuberculous mycobacteria infection

o. Mycobacterium tuberculosis, extrapulmonary

p. Progressive multifocal leukoencephalopathy

q. Recurrent septicemia (including non typhoid salmonella septicemia)

r. Lymphoma (Cerebral or B cell Non-Hodgkin)

s. Invasive cervical carcinoma

t. Atypical disseminated leishmaniasis

u. Symptomatic HIV-associated nephropathy or symptomatic HIV associated cardiomyopathy

WHO CASE DEFINITION FOR AIDS SURVEILLANCE IN ADULT WHERE HIV TESTING FACILITIES NOT AVAILABLE[18]

Case definition for AIDS is fulfilled if at least two major signs and one minor sign are present

Major signs:

a. Weight loss >10% of body weight

b. Chronic diarrhea >1 month

c. Prolonged fever >1 month

Minor signs:

a. Persistent cough >1 month

b. History of herpes zoster

c. Oropharyngeal candidiasis

d. Generalized lymphadenopathy

e. Chronic progressive herpes simplex infection

WHO GUIDELINES FOR INITIATION OF ART IN ADULTS AND ADOLESCENTS [18]

Table-2

Classification of HIV associated clinical disease	WHO clinical Stage	CD4 test not available or pending	CD4 test available
Asymptomatic	1	Do not treat	Treat if CD4 count < 200
Mild symptoms	2	Do not treat	Treat if CD4 count < 200
Advanced symptoms	3	Treat	Consider treating if CD4 ≤ 350 and initiate ART before CD4 drops below 200
Severe/Advanced symptoms	4	Treat	Treat irrespective of CD4 count

NACO GUIDELINES FOR INITIATION OF ART IN ADULTS AND ADOLESCENTS [6]

Table-3

CD4 count (cells/µL)	Actions
< 200	Treat irrespective of clinical stage
200 -350	Offer ART for symptomatic patients. Initiate treatment before CD4 drops below 200 cells/µL in asymptomatic patients
> 350	Defer treatment in asymptomatic persons

* If CD4 count is between 200- 250, this should be repeated in four weeks and treatment to be considered in asymptomatic patients.

British HIV association (BHIVA) suggests initiation of ART for asymptomatic HIV infected individuals having less than 200 CD4 T cell counts.[70] International AIDS society recommends initiation of ART in asymptomatic individuals with CD4 count > 200 to 350 cells / µl and viral load 50000 - 100000 copies / ml[20].

Ramalingam et al in a study conducted in 2001 have shown that mean CD4 counts in South Indian population both normal and HIV infected individuals are lower than in western population and have proposed a modified classification based on CD4 cell count for South Indians. The categories of CD4 count proposed were cell count >300, 81-300, ≤ 80 cells/µL, instead of the >500, 201-500, ≤ 200 recommended by CDC[21]

Kannagai et al in a study conducted in 2008 have shown that majority of HIV infected individuals in South India with CD4 counts of 200-350 cells/µL had higher viral load than that suggested by International AIDS Society.[22]

MICROALBUMINURIA[23,24]

DEFINITION

Microalbuminuria has been defined as Albumin excretion of 20 to 200 µg/min or 30-300 mg/day in a 24 hours urinary sample, anything above this level of excretion is called macroalbuminuria[25]. Microalbuminuria is also defined in terms of the urinary albumin to creatinine ratio greater than 30 mg/g in the first voided sample in the morning.

Table - 4

Definition of abnormality in albumin excretion			
Category	24-hrs collection (mg/24 hrs)	Timed collection (µg/min)	Spot collection (mg/gm cre)
Normal	< 30	< 20	< 30
Microalbuminuria	30 - 299	20 - 199	30 - 299
Clinical Albuminuria	≥ 300	≥ 200	≥ 300

PATHOPHYSIOLOGY OF MICROALBUMINURIA

The glomerular capillary wall (GCW) provides a barrier to filtration of large macromolecules. It has 3 components.

i. Endothelium of the capillary

ii. Basement membrane

iii. Epithelial cells (podocytes) surrounding the outer surface of the capillary basement membrane

Together these make up the filtration barrier, which despite the three layers filters several hundred times as much water and solutes as the usual capillary membrane. **Filterability of substance by glomerular capillaries decreases with increasing molecular weight.** The barrier to filtration is provided by 2 mechanisms:

Size selectivity and Charge selectivity

Size selectivity is a feature of the size of the pores of the components in the barrier. The endothelial cells have fenestrations with an approximate radius 40 nm and as such do not provide an effective barrier to albumin which has radius of 3.6 nm. The GBM has pores with a radius of 4 nm. Between the foot processes of epithelial cells a thin membrane called slit diaphragm provides barrier to filtration. The pores in the slit membrane are the same size as those in GBM. The GBM and slit diaphragm are therefore the major components of size selectivity.

Charge selectivity is provided by negatively charged anions such as Heparan sulphate, Proteoglycan which repel negatively charged

molecules such as albumin. These anions are present both in Endothelium and GBM which thus provide charge selectivity. The negative charge in the GBM also may be important for adhesion of epithelial cells, such that loss of negative charge may result in disruption of epithelial cell barrier, which in turn contributes to increased permeability to macromolecules such as albumin(due to loss of size selectivity).

When damage to the basement membrane or components of glomerular epithelial cells occurs, often the first manifestation is the appearance of plasma proteins in urine. Since albumin is the major circulating plasma protein and is relatively close in size to that of size selectivity, its appearance in the urine is the most sensitive indicator of damage or disruption of integrity of glomerular filtration barrier.

RENAL INVOLVEMENT IN HIV AND AIDS[26,27,28]

Several lines of evidence point to kidney disease as an important complication of human immunodeficiency virus (HIV) infection. Kidney function is abnormal in up to 30% of HIV–infected patients, AIDS-related kidney disease has become a relatively common cause of end-stage renal disease (ESRD) requiring dialysis, and kidney disease may be associated with progression to AIDS and death.[29]

Historical perspective

Rao et al[30] in 1984 described focal and segmental glomerulosclerosis in nine patients with AIDS and Nephrotic syndrome. The changes were similar to heroin induced nephropathy. Progression to End Stage Renal Disease (ESRD) in these patients was much more rampant. In the same year Pardo et al[31] reported a variety of glomerular changes seen at autopsy in patients with AIDS. Since then many reports have validated renal involvement in HIV infected population and a wide spectrum of renal syndromes have been reported.

Spectrum of renal disease

The renal manifestations of HIV infection occur commonly during all stages of infection. Renal manifestations of HIV infection occurs in 6-10% of seropositive individuals. A wide spectrum of renal syndromes has been associated with HIV infection.

Overview of HIV related renal disease

A. Acute Renal Failure

Pre renal

- Hypovolemia – [Diarrhoea, Vomiting, Bleeding, Pancreatitis]
- Hypoalbuminemia – [Severe malnutrition, Cirrhosis]

Renal

Mostly induced by drugs

- Acute Tubular Necrosis – [Aminoglycosides, Amphotericin-B, Foscarnet, Pentamidine, Rhabdomyolysis]
- Allergic Interstitial Nephritis – [Protease inhibitors, Phenytoin, Trimethoprim/Sulfamethoxazole, Cephalosporins]
- Crystal deposition – [Protease inhibitors, Acyclovir, Sulfadiazine]

Post renal

- External obstruction – [Tumour, Prostate hyperplasia, Urethral obstruction, Retroperitoneal fibrosis]
- Internal obstruction – [Crystal deposition, Blood clots, Tumour lysis]

B. Chronic Kidney Disease

Focal Glomerulosclerosis (Classic HIVAN)

Immune complex disease

- IgA nephropathy
- Mixed sclerotic immune complex nephropathy
- Proliferation glomerulosclerosis

Thromotic Microangiopathies

- Hemolytic Uremic Syndrome (HUS)

- Thromotic Thrombocytopenic Purpura (TTP)

Renal Amyloidosis

Renal parenchymal invasion by malignancies

[Lymphoma, Kaposi's sarcoma]

C. Fluid and Electrolyte disturbances

Hyponatremia

- Fluid loss
- SIADH
- Infection – Toxoplasmosis, Tuberculosis, Pneumocystis
- Adrenal insufficiency

Hyperkalemia

- Adrenal insufficiency
- Hyporeninemic Hypoaldosteronism
- IDDM [Pentamidine induced, Pancreatic cell dysfunction]
- Severe ARF

Hypokalemia

- GI losses
- Renal potassium wasting

Metabolic Alkalosis

- Upper GI loss
- Hypokalemia

Metabolic Acidosis

- Renal failure
- Septic shock
- Diarrhoea
- Drug induced interstitial nephritis

ACUTE RENAL FAILURE

The adults AIDS Clinical Trials Group has defined acute renal failure (ARF) in HIV-seropositive patients as a creatinine level greater than 1.5 mg/dL or a 1.3-fold increase above laboratory baseline that resolves within 3 months[29]. The fundamental aetiology and mechanisms involved in acute renal Injury in HIV patients are generally the same as in non HIV patients. Acute deterioration in renal function may be due to pre renal, intrinsic to renal tissue and post renal causes.

In overwhelming number of patients with ARF pre renal aetiology is noted. Pre renal causes of ARF include hypovolemic states due to profuse vomiting, diarrhoea, infections, sepsis and excessive & life threatening bleeding.

Intrinsic ARF in HIV infected patients may be due to hypovolemia, sepsis, shock and use of nephrotoxic agents for therapeutic and diagnostic purposes. Rhabdomyolysis, Use of NSAIDs, HUS & TTP are other causes of ARF.

Post renal ARF may be due to extra renal or distal obstruction. Intrinsic obstruction may also lead to post renal ARF. Outflow obstruction, retroperitoneal fibrosis and crystalluria may contribute to post renal ARF. Indinavir, Sulfadiazine and Acyclovir have been implicated in crystalluria[32].

FLUID & ELECTROLYTE DISORDERS

Among the electrolyte abnormalities observed in HIV patients, hyponatremia and hyperkalemia are significant.

Hyponatremia :-

- It is the most common, involving 30-60% of hospitalized symptomatic HIV and AIDS patients.
- Severe hyponatremia indicates poor prognosis[33].
- Volume depletion due to diarrhoea or vomiting is the usual cause of hyponatremia present at the time of hospital admission.
- Excess body water is attributed either to hypovolemia with physiologic stimulation of ADH, administration of hypotonic fluids or SIADH.

- SIADH is the usual culprit in those who develop hyponatremia during hospitalization[34].
- SIADH is usually associated with common pulmonary and intracranial diseases such as Pneumocystis pneumonia, Toxoplasmosis, Tuberculosis.
- AIDS patients have a high incidence of adrenal abnormalities. Adrenal pathology particularly CMV infection is found common in patients who have died from AIDS[35]. Other pathologic lesions that have been noted frequently include Hemorrhage, Toxoplasma infection, Cryptococcal infection, MAC, Infiltration with Kaposi's sarcoma and Lymphoma.

Hyperkalemia

Occurs as a result of

- High dose of Trimethoprim-Sulfamethoxazole or IV Pentamidine. The underlying mechanism with both drugs consists of inhibition of distal nephron sodium transport, leading to a decrease in distal potassium secretion. Trimethoprim shares structural similarity with the potassium sparing diuretic Triamterene.
- Hyperkalemia and hyponatremia may also be manifestation of mineralocorticoid deficiency due to adrenal insufficiency or the syndrome of hyporeninemic hypoaldosteronism[36].

- A systemic abnormality in potassium equilibrium which favours the development of hyperkalemia by a mechanism unrelated to renal potassium excretion, has also been identified in HIV infected individuals[37].

CHRONIC KIDNEY DISEASE

a) HIV Associated Nephropathy(HIVAN)

HIVAN represents a major complication of HIV infection. The evolution of HIVAN is the development of nephrotic syndrome initially and progress to ESRD in most patients[38].

HIVAN has become the most common single diagnosis in HIV infected patients with renal insufficiency. The true prevalence of HIVAN is not exactly known but in a study conducted in South Africa incidence of HIVAN was found to be 77-85% in patients with persistent microalbuminuria. The geographic distribution of HIVAN is variable and depends on specific risk factors such as race, gender and drug use.

HIVAN is recognized throughout the spectrum of HIV disease. It can be the first manifestation of HIV infection or even precede detection of HIV antibodies[39]. Symptomatic HIVAN is now classified as clinical stage 4 disease by the WHO[40]. There is a marked racial predilection for the

development of HIVAN, as over 90% of patients are black, with a male predominance[41]. 30-60% of people with HIVAN are intra venous drug abusers[42]. The remainders are either homosexual or originate from regions where HIV infection is endemic. In approximately 10% of patients no specific risk factors of HIV can be identified.

Unfortunately, most patients who develop HIVAN do not have early signs or symptoms that would provide a clue to this diagnosis prior to the onset of progressive nephropathy. It is characteristically a disease in those of African descent and is less common in Europe and Asian populations[43,44,45,46].

Pathogenesis:-

The pathogenesis of HIVAN has been studied intensely over the past 15 years. The question in the pathogenesis of HIVAN is whether the disease can be attributed to direct viral effect or to HIV related changes on the cytokine milieu. HIVAN is caused by HIV gene expression in renal tissue, resulting in injury of glomerular and tubular epithelial cells.

Early studies using in situ hybridisation to a C-DNA probe found the HIV genome in tubular and glomerular epithelial cells in patients with HIVAN. Patient with immune mediated glomerulonephritis or HIV infected patients with no renal disease had less cellular involvement.

Since HIV proliferation appears to be major determinant of cytotoxicity, factors that precipitate viral replication within the kidney

could explain the sudden onset of the disease. Circularized viral DNA, a marker of recent nuclear import of full-length, reverse-transcribed RNA, was detected in the biopsies, suggesting active replication of HIV in renal tissue[47]. HIV proliferation is regulated by two genes **nef** and **vif** with opposing action. Minor mutations in either of these lead to rapid viral replication and death of the host cells. Others genes implicated are **vpr**, **tat** and **rev.** Concomitant infection with Viral hepatitis, Syphilis or CMV, could induce HIV replication. CMV may promote viral proliferation through a mechanism that is dependent on tumour necrosis factor (TNF)[48].

HIV is a potent stimulator of TGF β, a cytokine strongly implicated in development of fibrosis. The transgenic mice model (Tg 26) suggests that activation of cytokine could be the basis for the extensive interstitial fibrosis and glomerular scleorsis that are hallmark of HIVAN[49].

HIV RNA and protein markers specific for HIV have been demonstrated in tubular epithelium, glomerular epithelial cells and mesangial cells by a variety of techniques in vitro and in renal biopsy tissue of HIV patients[50].

In transgenic mice model (Tg 26), HIV-1 envelope (gp 41 and gp 120) and regulatory genes are expressed but gag and pol genes are deleted to render the virus non infectious. These mice develop a syndrome closely resembling HIVAN[51]. Kidneys were transplanted between normal and transgenic mice. HIVAN then developed in non transgenic mice, where as

the normal kidneys remained disease free in transgenic mice. This study provides evidence that HIVAN is caused by a direct HIV gene expression rather than the systemic effects of HIV infection[52].

HIV infection may involve epithelial cells from multiple segments of the nephron including glomerulus (podocytes), tubule, thick ascending loop of Henle and collecting duct. This pattern of involvement may explain the tubular dilatation seen in kidney biopsy of patients with HIVAN[53]. HIV-infection induces loss of contact inhibition[54] and loss of podocyte differentiation markers and increases podocyte proliferation[55,56]. In addition, HIVAN showed a marked reduction in the expression of cyclins and cyclin-dependent kinase inhibitors which may account for the activation of podocyte proliferation in collapsing nephropathy[57,58].

The kidney also seems to be the reservoir for HIV. Despite undetectable viral levels in serum, a case report described in a patient who continued to express HIV in renal epithelial cells determined by RNA in situ hybridization[59]. There is also compelling evidence that active replication of HIV occurs in kidney epithelium, possibly producing HIV strains in the kidney microenvironment that differ from HIV circulating in the blood. This suggests that kidney may serve as a viral reservoir harbouring HIV strains that have evolved under tissue specific selection process[60].

Histopathology[61]:-

HIVAN is associated with characteristic glomerular, tubular, interstitial and ultra structural lesions. Autopsy data demonstrates that 90% of patients with the clinical diagnosis of HIVAN have focal and segmental glomerulosclerosis[34].

Histopathologically classic HIVAN is a collapsing form of focal segmental glomerulosclerosis with podocyte hyperplasia and dedifferentiation associated with severe tubulopathy which is characterized by tubular apoptosis, microcytes and interstitial fibrosis.

Light Microscopic Features:-

- Collapsing Focal Segmental Glomerulosclerosis(FSGS) or mesangial hyperplasia.
- Cystic tubular dilatation.
- Interstitial oedema.
- Cellular infiltration by T- lymphocytes or monocytes.
- Dilated degenerating proximal tubules filled with eosinophilic material possibly representing cast formation in situ.

Electron Microscopy Features:-

- The presence of numerous tubuloreticular inclusions within the endothelial cells is an important finding in HIVAN. Finding numerous tubulointerstitial inclusions in capillary endothelial cells

in a patient with FSGS prompts some pathologists to request for HIV antibody testing.

Although renal tissue may stain for IgM, C1q, C3 and kappa (κ) or lambda (λ) light chains in areas of focal sclerosis, immunologic mechanisms are probably not central to genesis of HIVAN[62].

Clinical Presentation

- Proteinuria but no hematuria.
- Progressive renal failure
- Absence of oedema or hypertension (due to volume depletion)
- Proteinuria usually in nephrotic range (ranging from 1.7 – 40 gm/day) - hallmark of HIVAN[63].

Investigation

- Urine analysis: Often reveals severe proteinuria 2+ and more with oval fat bodies and frank lipiduria, presence of renal tubular epithelial cells in the urinary sediment. Broad waxy casts are also seen.
- Microalbuminuria: Seen in 9-30% of untreated HIV patients in very early stages of disease course.
- Azotemia.
- Renal Ultrasound: Normal or enlarged kidneys with increased echogenicity.
- Renal Biopsy: Reveals characteristic findings.

Management:-

Patients with HIVAN may experience rapid progression to ESRD. HAART delays progression to ESRD[64], although a proportion of patients will still require renal replacement therapy despite HAART[65]. The incidence of HIVAN has decreased considerably in the HAART era, with risk reductions of approximately 60% in a multivariate analysis[66].

Available treatments options are

- Anti Retroviral Therapy
- Corticosteroids
- ACE inhibitors or ARBs

Anti Retroviral Therapy:-

Because HIV infection itself appears to be the cause of HIVAN, antiretroviral therapy is a logical choice as a therapy for HIV-related renal diseases. There appears to be a more beneficial effect of triple combination over Zidovudine monotherapy[67]. PI-containing HAART had a lower rate of decrease in creatinine clearance compared with earlier monotherapy or dual therapy[67]. Direct beneficial effects of PIs on HIV-related kidney disease may include inhibition of apoptosis and superoxide generation, interference with the production and release of inflammatory cytokines and chemokines, and down-regulation of endothelial cell expression of adhesion molecules crucial in mediating leukocyte recruitment to sites of

inflammation[68,69,70]. In addition to being effective in treating established HIVAN, ART may decrease the actual incidence of de novo HIVAN[66,71].

Corticosteroids:-

In patients with progression despite HAART, corticosteroids are recommended on the basis of retrospective and prospective studies showing benefit[29]. In a large retrospective cohort analysis, corticosteroid therapy was associated with an improvement in creatinine clearance over time (+3.32 mL/min/month), compared with a deterioration (−5.57 mL/min/month) in non–corticosteroid treated subjects[67]. One prospective, open-label study in patients receiving monotherapy or dual antiretroviral therapy showed a decrease in serum creatinine levels(mean decrease, 8.1-3.0 mg/dL) and 24-hour urinary protein excretion (mean decrease, 9.1-3.2 gm/day) with glucocorticoid therapy and infectious complications were infrequent[72].

ACE inhibitors:-

Angiotensin II increases the cellular synthesis of TGF β which has been implicated in the pathogenesis of HIVAN. ACE inhibitors are effective in slowing the progression of renal insufficiency by reducing production of TGF β in both humans and HIV transgenic mice[73]. Multivariate analysis revealed a reduced risk of renal failure, greater overall survival, improved creatinine levels, and stabilization of proteinuria associated with ACE inhibitors with no difference in exposure to

antiretroviral therapy[74]. Current guidelines reserve ACE inhibitor use to the subset of individuals with hypertension and proteinuria, with the goal of keeping blood pressure less than 125/75 mm Hg, in line with the K/DOQI recommendations for HIV-negative CKD[29].

Renal biopsy should be offered to patients as treatment and prognosis vary according to the biopsy results.

Risk factors for progression of renal disease include

- Lower CD4 count.
- Detectable HIV RNA levels.
- Hypertension.
- Hypoalbuminemia.
- Elevated serum creatinine.

b) Non HIVAN causes of CKD.

Non-HIVAN causes of CKD are more likely to occur in individuals who are not black, are normotensive, are hepatitis B coinfected, and have higher CD4 cell counts[65].

i. Immune Complex Disease

HIV associated immune mediated renal disease is the most common glomerular disease found on renal biopsy in series reported from Italy and France[75,76].

Important forms of HIV immune complex disease are

- IgA nephropathy
- Membrano Proliferative glomerulopathy
- Lupus like nephropathy
- Membranous nephropathy
- Minimal change disease

HIV has been implicated as a stimulus for immune complex formation. Immune complexes with antigen have been identified in the circulation and the renal tissue. Complexes contain HIV antigen and antibody to gp 120, immunoglobulins, C1q and C3. Interstitial infiltrates are frequent with a higher frequency of B cells than in HIVAN and the progression to renal failure is slower than in HIVAN[77]. Renal biopsy is important in determining the histological diagnosis in patients with HIV infection and renal disease, including those who present with nephrotic range proteinuria and is the only definitive way to diagnose HIVICD[65,79]. In a recent U.S. multicenter observational study, patients with renal diseases other than HIVAN had a longer course until the development of ESRD and had better overall survival[65]. No differential effect of treatment with antiretroviral drugs was noted in the group of patients without HIVAN.

ii. Thrombotic Microangiopathies

May present as Haemolytic Uremic Syndrome (HUS) or Thrombotic Thrombocytopenic Purpura (TTP).

The diseases manifest their common presentations, but because of the protean manifestations of HIV infection, may prove difficult to diagnose. Abnormalities of the peripheral blood smear remain the criterion for making the diagnosis[79]. Although a variety of different therapeutic approaches have been employed, plasmapharesis remains the safest and perhaps the most effective treatment for HIV-infected patients with TTP[80]. The potential therapeutic role of antiretroviral therapy in such cases, while attractive on theoretical grounds has not been tested adequately in well-designed clinical studies.

END STAGE RENAL DISEASE

HIVAN has become the third leading cause of ESRD among African Americans aged 20-64 yrs[17,34]. Black patients infected with HIV are at risk for the development of ESRD, irrespective of mode of viral acquisition.

Management options include

- Renal replacement in the form of Haemodialysis or Peritoneal Dialysis.

- Transplantation - Transplant in HIV-positive individuals is associated with higher serum creatinine levels and a greater incidence of rejection. On the basis of existing literature, it is reasonable for HIV-positive patients with ESRD to be offered living donor or deceased donor renal transplant if they have had an undetectable HIV viral load and a stable CD4 cell count of more than 200/μL for 6 months and are free of active opportunistic infections[81].

MICROALBUMINURIA IN HIV AND AIDS PATIENTS

Microalbuminuria is an independent and earliest marker of renal involvement and loss of endothelial integrity. Overall microalbuminuria is seen in ~ 20% (varying from 8.7% to 30% in various studies) of untreated HIV infected patients[5,6,7,8,9,10] and significant proteinuria in 6%[82]. Microalbuminuria levels showed correlation with CD4 T cell count suggesting an association between progression of disease and microalbuminuria. Various studies were conducted to find out the incidence of microalbuminuria in HIV infected patients[8,9].

Luke et al noticed abnormal urinary levels of microalbuminuria in 19.4% of HIV positive patients[9]. Microalbuminuria did not correlate with race, sex, risk factor of AIDS, disease history or concurrent drug therapy.

In contrast, urinary microalbumin levels correlated well with CD4 T cell and viral load suggesting an association between AIDS progression and microalbuminuria.

Busch et al[8] study found that albuminuria occurred frequently with CD4 counts below 200/μL and also concluded that subclinical renal involvement is not uncommon in HIV infection with T4 cell counts > 200/ μL.

Present study was undertaken to investigate microalbuminuria in HIV patients in South India where investigators have shown that at CD4 counts between 200-350/μL South Indians have higher viral load than that suggested by International AIDS Society.

MATERIALS AND METHODS

Setting: This study was carried out at **Government Kilpauk Medical College & Hospital, Chennai .**

Collaborating department: ART Centre & Department of Internal Medicine.

Study design **:** Cross Sectional Study

Period of study **:** January 2008 - September 2008

Sample size **:** 80 cases

Ethical Committee Approval **:** Obtained

Informed Consent **:** Obtained

Conflict of Interest **:** There was no conflict of interest

Financial Support **:** Nil

Selection and details of study subjects:

The study was conducted in HIV positive patients who were attending the ART clinic, Government Kilpauk Medical College & Hospital, Chennai.

Inclusion criteria:

Adult male & non pregnant female HIV infected patients before ART therapy.

Exclusion criteria:

- Children
- Overt renal disease
- Diabetes mellitus
- Systemic hypertension
- Collagen vascular disease
- Urinary tract infection
- Hepatitis
- Patients on nephrotoxic agents
- Patient not willing for study

The total number of HIV positive patients screened were 270, of which 90 patients had Tuberculosis infection (pulmonary & extra pulmonary) and they were on Anti Tuberculosis Treatment, so they were excluded from study. 35 patients who had Diabetes Mellitus were excluded from the study.

27 cases were associated with Systemic Hypertension and hence where excluded from the study. The patients with NSAID abuse were found to be 16 in numbers and they were excluded from study. 10 patients were found to be having Overt Renal Disease and they were excluded from the study. 12 patients had Urinary Tract Infection evidenced by urinary examination and they were excluded from the study.

After exclusion of these patients, the number of patients selected for our study was 80. They were divided into 2 groups according toCD4 count. 40 patients with CD4 count of ≤ 350 cells/ μL were grouped as Group A. Similarly 40 patients with CD4 count of > 350 cells/μL were grouped as Group B.

LIMITATION

1. Due to technical and financial constraints only 80 cases could measured for microalbuminuria.
2. Only microalbuminuria & 24 hours urinary protein was measured.
3. Renal biopsy was not attempted due to ethical reason.
4. Long term follow up was not attempted.
5. Effect of ART on microalbuminuria was beyond the purview of the study.
6. Viral load could not be estimated due to constraints.

METHODOLOGY

Selected socio-demographic, clinical data were elicited and few necessary investigations were done and data was recorded in a profoma.

I. Socio – demographic data:

Age

Sex

Occupation

II. Clinical data:

Clinical examination

WHO clinical staging

III. Laboratory data:

HB% TC DC: P L E M B ESR

URINE: ALBUMIN SUGAR DEPOSITS

BLOOD: SUGAR UREA

SERUM: CREATININE ELECTROLYTES - Na+ K+

SERUM: BILIRUBIN SGOT SGPT

ALKALINE PHOSPHATASE

URINE: MICROALBUMIN & ALBUMIN CREATININE RATIO

24 hr urine was collected. Patients were advised to avoid strenuous exercise, high protein diet during the period of collection of urine sample Albumin level in urine was measured by Immunoturbidometry technique[83]. Creatinine levels were measured using Jaffe method.

24 HOURS URINE PROTEIN. .

CD4 COUNT:

CD4 count was done using flow cytometry[84]. A computer calculates the number of CD4 T cells by analyzing the size of the cell and which of the antibodies it has been tagged with. The overall process is called Fluorescence Activated Cell Sorting (FACS)[85].

CHEST X-RAY

ECG

USG – ABDOMEN & KUB

IV. Statistical analysis

Data was entered in Microsoft excel spread sheet and analyzed statistically using SPSS software version 11.5.

Following tests were used to check for statistical significance.

1. Two sample independent‘t’ test.
2. Mann-Whitney U rank non – parametric test.
3. Chi-Square test.
4. Binary Logistic Regression Model.

Results were considered significant if the ‘p’ value was below 0.05.

REFERENCE VALUE USED IN THIS STUDY

BMI [80]

Body Mass Index = Weight (kg) / Height (m^2).

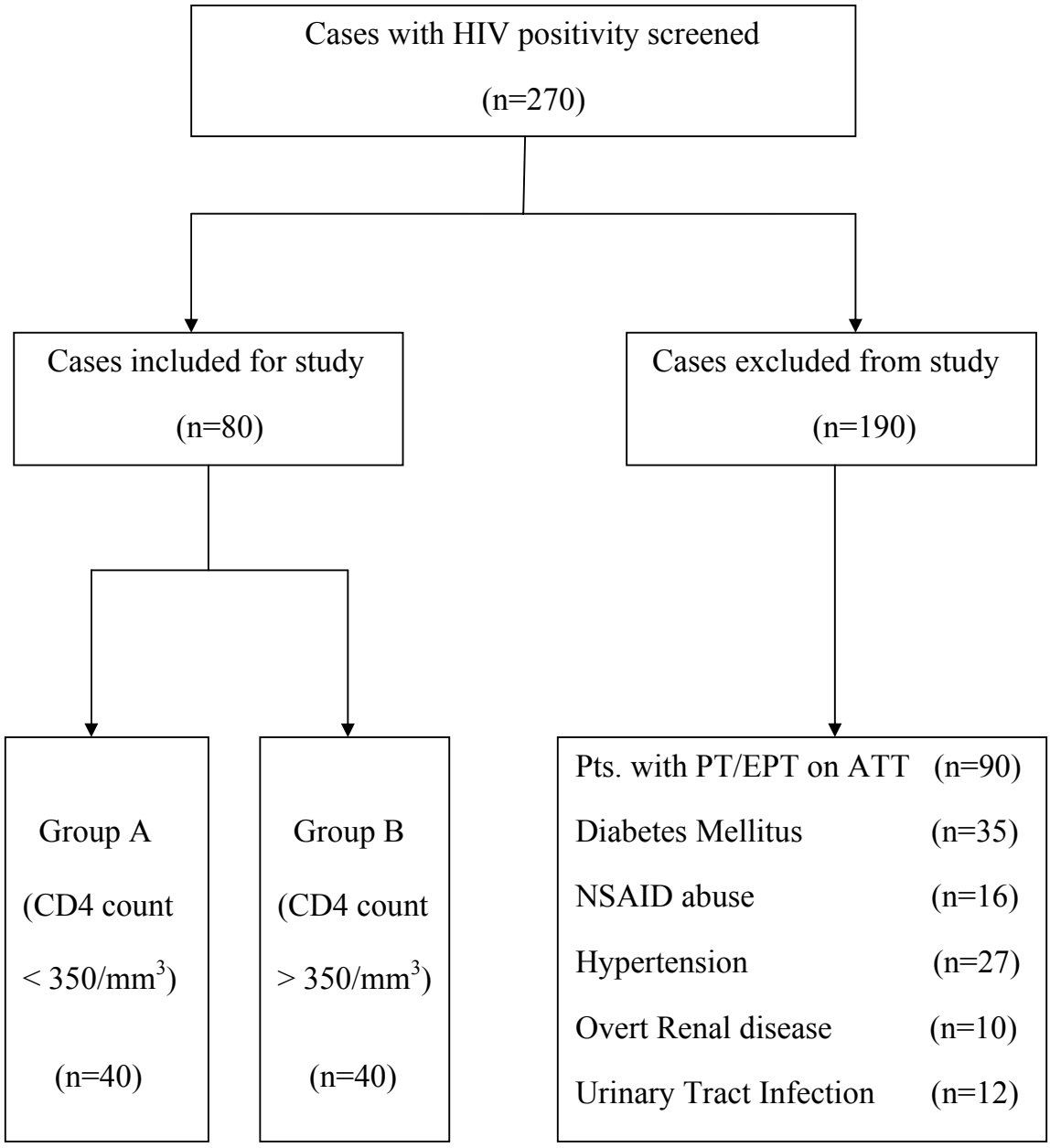
Values 18.5 - 22.9 kg / m^2 was taken as normal weight

< 18.5 kg / m^2 was taken as underweight

23- 24.9 kg / m^2 was taken as overweight

≥ 25 kg / m^2 was taken as obesity

CASES SCREENED – FLOW CHART



RESULTS

- A total of 80 HIV seropositive patients were studied. They were divided into two groups.
- Group A included 40 HIV seropositive patients with CD4 cell count ≤ 350/ μL (n=40)
- Group B included 40 HIV seropositive patients with CD4 cell count > 350/ μL (n=40)
- Mean CD4 count of study group was 387.7 ± 193.78 cells/μL (Group A – 236.75 ± 79.77 cells/μL. Group B – 538.65 ± 151.53 cells/μL.)
- Out of 80 patients 41 (51.25%) were males (Group A – 21, Group – B 20) and 39 (48.75%) were females (Group A -19, Group B – 20)
- Mean age group of study population was 33.85 ± 8.26 years (Group A – 35.65 ± 9.80 years. Group B – 32.05 ± 6.46years)
- House wives and others constituted the majority of study group occupation about 35% and 40% respectively.
- Heterosexual route was the most common mode of transmission of HIV infection about 91.25%.
- Mean BMI of study group was 21.66 ± 3.33 kg/m^2 (Group A – 19.92 ± 2.65 kg/m^2. Group B 22.4 ± 4.02 kg/m^2)
- None of the patients in study group had symptoms pertaining to renal pathology.

- ❖ Nine patients (11.25%) (Group A - 9; Group B - 0) had Microalbuminuria.
- ❖ Six patients (7.5%) (Group A - 6; Group B - 0) had Overt proteinuria.
- ❖ Eight patients (10%) (Group A - 7; Group B - 1) had elevated levels of Serum Creatinine.
- ❖ Significant correlation was found between microalbuminuria and CD4 count,
- ❖ No significant correlation was found between microalbuminuria and Age, Sex, Body Mass Index & WHO staging.

CD4 GROUP

Table - 5

CD4 Group	Number of patients	CD4 count cells/µL	MeanCD4 count cells/µL
A	40	≤ 350	236.75 ± 79.77
B	40	> 350	538.65 ± 151.53
Total	80		387.70 ± 193.78

Mean CD4 count of Group A was 236.75 ± 79.77 cells/µL.

Mean CD4 count of Group B was 538.65 ± 151.53 cells/µL.

AGE DISTRIBUTION AND CD4 COUNT

Table – 6 A

Age Group	CD4 Group		Total
	A	B	
21 – 30	17 (42.5%)	21 (52.5%)	38 (47.5%)
31 – 40	12 (30%)	16 (40%)	28 (35%)
41 – 50	9 (22.5%)	2 (5%)	11 (13.75%)
> 50	2 (5%)	1 (2.5%)	3 (3.75%)
Total	40 (100%)	40 (100%)	80 (100%)

Table – 6 B

CD4 Group	AGE	
	Mean	SD
A	35.7	9.8
B	32.1	6.5

p value = 0.163 Not significant.

Mean age of Group A was 35.65 ± 9.80 years.

Mean age of Group B was 32.05 ± 6.46 years.

There was no statistically significant difference in distribution with respect to Age between two groups.

SEX DISTRIBUTION AND CD4 COUNT

Table-7

SEX	CD4 GROUP		TOTAL
	A	B	
MALE	21 (52.5%)	20 (50%)	41 (51.25%)
FEMALE	19 (47.5%)	20 (50%)	39 (48.75%)

p value = 0.823. Statistically not significant.

There was no statistically significant difference in the distribution with respect to Sex between two groups.

AGE DISTRIBUTION IN RELATION TO SEX AND CD4 COUNT

Table – 8

Age Group	Group A		Group B	
	Male	Female	Male	Female
21 – 30	7	10	10	11
31 – 40	7	5	7	9
41 – 50	5	4	2	0
> 50	2	0	1	0
Total	21	19	20	20

p value for Group A = 0.41 Not significant.

p value for Group B = 0.35 Not significant.

This table shows that there is no statistically significant difference in distribution with respect to Age & Sex within each Group.

OCCUPATION DISTRIBUTION AND CD4 COUNT

Table-9

Occupation	Total
House wife	28 (35%)
Coolie	17 (21.25%)
Watchman	2 (2.5%)
Driver	1 (1.25%)
Others	32 (40%)
Total	80 (100%)

WHO STAGING - DISTRIBUTION AND CD4 COUNT

Table – 10

WHO Staging	CD4 count		Total
	A	B	
1	16 (40%)	35 (87.5%)	51 (63.75%)
2	9 (22.5%)	2 (5%)	11 (13.75%)
3	13 (32.5%)	3 (7.5%)	16 (20%)
4	2 (5%)	0	2 (2.5%)
Total	40 (100%)	40 (100%)	80 (100%)

p value = 0.000 Significant.

There was statistically significant difference in the distribution with respect to WHO staging between two groups.

ROUTE OF TRANSMISSION – DISTRIBUTION

Table – 11

Route of Transmission	Total
Heterosexual	73 (91.25%)
Blood Transfusion	3 (3.75%)
Intravenous Drug User	2 (2.5%)
Others	2 (2.5%)

BMI GROUP – DISTRIBUTION AND CD4 COUNT

Table-12A

BMI Group (kg / m2)	CD4 Group		Total
	A	B	
< 18.5	5 (12.5%)	4 (10%)	9 (11.25%)
18.5 - 22.9	29 (72.5%)	18 (45%)	47 (58.75%
23 - 24.9	4 (10%)	11 (27.5%)	21 (26.25%)
≥ 25	2 (5%)	7 (17.5%)	3 (3.75%)
Total	40 (100%)	40 (100%)	80 (100%)

p value = 0.033 Significant.

There was statistically significant difference in distribution with respect to Body Mass Index between two groups.

Table – 12B

CD4 Group	Body Mass Index (kg/m^2)	
	Mean	**SD**
A	19.91	2.65
B	22.4	4.02

p value = 0.002 Significant.

Mean BMI of Group A patients was 19.91 ± 2.65 kg/m^2.

Mean BMI of Group B patients was 22.40 ± 4.02 kg/ m^2.

Body Mass Index was lower in patients with CD4 Group A compared to Group B indicating a possible direct proportional relation between CD4 count & BMI.

MICROALBUMINURIA

DISTRIBUTION IN RELATION TO CD4 COUNT

Table – 13A

Microalbuminuria	CD4 Group		Total
	A	B	
Absent	31 (77.5%)	40 (100%)	71 (88.75%)
Present	9 (22.5%)	0	9 (11.25%)
Total	40 (100%)	40 (100%)	80 (100%)

p value = 0.001 Significant

This table shows statistically significant difference in distribution of prevalence of microalbuminuria with CD4 count. 9 out of 40 patients in Group A with CD4 count ≤ 350 had microalbuminuria. None of the patients in Group B with CD4 count > 350 had microalbuminuria.

Table – 13 B

CD4 Group	Urine Microalbumin (mg/day)	
	Mean	SD
A	37.95	33.75
B	12.13	5.96

p value = 0.000 Significant.

Mean value of urine microalbumin in Group A is 37.95 ± 33.75 mg/day.

Mean value of urine microalbumin in Group B is 12.13 ± 5.96 mg/day.

DISTRIBUTION IN RELATION TO AGE & SEX

Table – 14

Age Group	Group A	
	Male	Female
21 – 30	1	2
31 – 40	3	1
41 – 50	0	1
> 50	1	1
Total	5	4

p value = 0.35 Not significant

There is no statistically significant difference in distribution of prevalence of microalbuminuria with respect to Age & Sex in Group A patients.

URINE ALBUMIN CREATININE RATIO DISTRIBUTION IN RELATION TO CD4 GROUP

Table – 15

CD4 Group	Urine Albumin Creatinine Ratio (mg/gm)	
	Mean	SD
A	36.78	31.86
B	13.4	5.86

p value = 0.000 Significant.

Mean urine albumin creatinine ratio of Group A was 36.78 ± 31.86 mg/gm.

Mean urine albumin creatinine ratio of Group B was 13.40 ± 5.86 mg/gm.

OVERT PROTEINURIA DISTRIBUTION IN RELATION TO CD4 GROUP

Table – 16 A

Overt Preoteinuria	CD4 Group		Total
	A	B	
Absent	34 (85%)	40 (100%)	74 (92.5%)
Present	6 (15%)	0	6 (7.5%)
Total	40 (100%)	40 (100%)	80 (100%)

p value = 0.011 Significant.

This table shows statistically significant difference in distribution of prevalence of overt proteinuria with CD4 count. 6 out of 40 patients in Group A with CD4 count ≤ 350 had overt proteinuria. None of the patients in Group B with CD4 count > 350 had overt proteinuria.

Table – 16 B

CD4 Group	24 Hours Urine Protein (mg/day)	
	Mean	SD
A	227.98	104.37
B	144.18	43.42

p value = 0.000 Significant.

Mean 24 hours urine protein level in Group A is 227.98 ± 104.37 mg/day.

Mean 24 hours urine protein level in Group B is 144.18 ± 43.42 mg/day.

SERUM CREATININE DISTRIBUTION IN RELATION TO CD4 GROUP

Table – 17 A

Serum Creatinine	CD4 Group		Total
	A	B	
Elevated	7 (17.5%)	1 (2.5%)	8 (10%)
Normal	33 (82.5%)	39 (97.5%)	72 (90%)
Total	40 (100%)	40 (100%)	80 (100)

p value = 0.025 Significant.

There is statistically significant difference in distribution of prevalence of elevated serum creatinine levels between two groups.

Table – 17 B

CD4 Group	Serum Creatinine (mg/dl)	
	Mean	SD
A	0.89	0.19
B	0.83	0.09

p value = 0.056 Not significant.

Though there is statistically significant difference in distribution of prevalence of elevated creatinine levels, difference is not significant in actual distribution.

BLOOD UREA DISTRIBUTION IN RELATION TO CD4 GROUP

Table – 18

CD4 Group	Blood Urea (mg/dl)	
	Mean	**SD**
A	24.45	7.84
B	21.2	3.77

p value = 0.021 Significant.

There was statistically significant difference in distribution with respect to blood urea between two groups.

Mean blood urea level in Group A was 24.45 ± 7.84 mg/dL.

Mean blood urea level in Group B was 21.20 ± 3.77 mg/dL.

BLOOD SUGAR DISTRIBUTION IN RELATION TO CD4 GROUP

Table – 19

CD4 Group	Blood Sugar (mg/dl)	
	Mean	**SD**
A	89.55	21.48
B	87.73	18.25

p value = 0.683 Not significant.

There was no statistically significant difference in distribution with respect to blood sugar between two groups.

SERUM SODIUM DISTRIBUTION IN RELATION TO CD4 GROUP

Table – 20

CD4 Group	Serum Sodium (meq/L)	
	Mean	**SD**
A	139.63	2.65
B	139.18	2.24

p value = 0.414 Not significant.

There was no statistically significant difference in distribution with respect to serum sodium between two groups.

SERUM POTASSIUM DISTRIBUTION IN RELATION TO CD4 GROUP

Table - 21

CD4 Group	Serum Potassium (meq/L)	
	Mean	**SD**
A	3.84	0.53
B	3.9	0.17

p value = 0.476 Not significant.

There was no statistically significant difference in distribution with respect to serum potassium between two groups.

BINARY LOGISTIC REGRESSION MODEL

This test was applied to all the patients to assess the correlation of various risk factors with microalbuminuria.

Dependent variable: Microalbuminuria.

Risk factors assessed: Age, Sex, Body Mass Index, WHO staging and CD4 count.

Risk factor significant: **CD4 count.**

Table - 22

Name of the variable	**p value**	**Odds ratio**
Age	0.733	0.795
Sex	0.782	1.016
WHO Staging	0.789	1.132
Body Mass Index	0.208	1.192
CD4 count	**0.011**	**0.99**

From the above table it is evident that CD4 count alone correlates with prevalence of microalbuminuria in our study group. Prevalence of microalbuminuria increases as CD4 count comes down. In our study microalbuminuria is seen in patients with CD4 count ≤ 350 cells/μL with a prevalence rate of 11.25%.

DISCUSSION

HIV infection is the pandemic of modern era. Renal disorders are encountered in all stages of HIV infection.

Microalbuminuria is the earliest marker of the renal involvement, seen in approximately 20% (8.7-30% in various studies) of untreated HIV infected patients[5,6,7,8,9,10.].

HIVAN has become the third leading cause of ESRD among African Americans aged 20-64 years[17,34].

Ramalingam et al[21] in a study conducted in 2001 have shown that mean CD4 counts in South Indian population, both normal and HIV infected individuals are lower than in western population and have proposed a modified classification based on CD4 cell count for South Indians. The categories of CD4 count proposed were cell count > 300, 81-300, ≤ 80 cells/μL, instead of the > 500, 201-500, ≤ 200 recommended by CDC.

Kannagai et al[22] in a study conducted in 2008 have shown that majority of HIV infected individuals in South India with CD4 counts of 200-350 cells/μL had higher viral load than that suggested by International AIDS Society.

Present study was undertaken based on above observations. There are no supportive studies showing the comparison of prevalence of microalbuminuria in CD4 counts ≤ 350/µL & > 350/µL.

MICROALBUMINURIA

Luke DR et al[9] observed that microalbumin levels did not correlate with age or sex. In our study also there was no correlation of microalbumin levels with age or sex.

The prevalence of microalbuminuria in HIV and AIDS patients differ in various studies. Morten Baekken et al[6] study showed microalbuminuria in 8.7% of HIV infected patients. Lynda Anne Szczech et al[7] study showed that microalbuminuria was present in 11% of HIV infected patients. Busch HW et al[8] study showed microalbuminuria in 13% of HIV patients. Luke DR et al[9] study noted 19.4% of HIV patients had microalbuminuria. Kimmel PL et al[10] study showed microalbuminuria in 20 to 30% of HIV patients.

In our study the prevalence of microalbuminuria was found to be 11.25%. All the 9 patients who had microalbuminuria belonged to Group A. The mean urine microalbumin level was 37.95 mg/day (SD 33.75).

URINE ALBUMIN CREATININE RATIO

Kimmel PL et al, Umana WO et al[87] noticed that, the prevalence of an increased urine albumin creatinine ratio amounting to microalbuminuria was 29.8% in the HIV infected patients. In Busch HW et al[8] study, the prevalence rate was 13.4%. In Lynda Anne Szczech et al[7] study, the prevalence rate was 11%.

In our study the prevalence of elevated urine albumin creatinine ratio amounting to microalbuminuria was seen in 11.25% of study group. All the 9 patients who had elevated urine albumin creatinine ratio belonged to Group A. The mean urine albumin creatinine ratio is 36.78 mg/gm (SD 31.86).

OVERT PROTEINURIA

Several studies have suggested that abnormality of protein excretion without frank nephritic syndrome is common in HIV infected populations. In Agaba EL et al[88] study proteinuria was detected in 25.3% Of HIV patients. In Cravley ST et al[89] study the prevalence of asymptomatic proteinuria was 14% and the presence of proteinuria did not correlate with viral load. Varma PP et al[90] study showed overt proteinuria in 17.6% of HIV patients. In Gardener et al[91] study overt proteinuria was present in 11.2% of HIV seropositive women. Lynda Anne Szczech[92] et al

study showed overt proteinuria in 14.1% of HIV seropositive women. Amitis Ramezaniab et al[93] study showed overt proteinuria in 12.3% of HIV infected persons.

In our study, 7.5% of the study group had overt proteinuria. All the 6 patients with overt proteinuria belonged to Group A. Mean urine 24 hours urine protein was 227.98 mg/day (SD 104.37).

CORRELATION OF MICROALBUMINURIA

Various studies show that there is a strong correlation between CD4 count and microalbuminuria level. Szczech LA et al[94], Busch HW et al[8] and Atta MG et al[95] studies confirmed that microalbuminuria is commonly seen with CD4 counts ≤ 200/μL. Busch HW et al[8] in their study also concluded that subclinical renal involvement is not uncommon in HIV infection with T4 cell counts > 200/μL.

In our study 9 out of 80 patients had microalbuminuria and all the patients with microalbuminuria were found to have CD4 count ≤ 350/μL and no patients with CD4 count > 350/μL had microalbuminuria.

Binary logistic regression model was applied to all patients to assess correlation of various risk factors with prevalence of microalbuminuria. Statistically significant correlation was seen between

prevalence of microalbuminuria and CD4 count. Microalbuminuria was not correlating with Age, Sex, WHO staging and Body Mass Index.

UREA & CREATININE

In our study abnormal levels of serum creatinine not amounting to renal failure was found in 4 male and 4 female patients, of which 7 were found to have CD4 count ≤ 350/μL. There was statistically significant difference between distributions of blood urea with respect to CD4 group.

Though there was biochemical evidence of mild renal failure, they did not reveal any symptoms related to renal involvement. Thus this study showed that HIV infected and AIDS individuals may have asymptomatic renal involvement.

No electrolyte abnormalities were seen in our study. However the review of literature showed that the commonest fluid and electrolyte abnormality seen in HIV and AIDS cases is hyponatremia.

Behar DM et al[96] and Winston JA[97] et al studies show that type of renal involvement varied in different geographic regions. Studies in USA have shown high prevalence of Classical HIVAN. European studies from the United Kingdom and Italy emphasize a high proportion of patients with nephrotic syndrome in the setting of HIV infection have glomerulonephritis[76,98] . A study from Thailand of HIV infected patients

with renal disease reported a diverse set of glomerulonephritis, but no cases of classic HIVAN[46].

Christina M. Wyatt in her publication has mentioned about racial disparities in renal manifestations of HIV infection[99]. While in general, patients of African heritage are more likely to have HIVAN, European and Asian populations more often appear to have glomerulonephritis[45,46,75,98].

Gardener, Lytt I et al[91], showed proteinuria or elevated serum creatinine in HIV infected women were associated with an increased risk of death after controlling the other risk factors.

HIV infection is well known to involve kidneys and moderate to severe renal involvement has shown to worsen the HIV status, hence HIV infected patients have to be closely monitored for their renal involvement in its early phase and managed appropriately.

SUMMARY

The present study was aimed to study the prevalence of microalbuminuria in HIV seropositive patients and also to find out its correlation with CD4 counts. With rigid criteria 80 HIV seropositive cases were selected. There were 41 males and 39 females in the study group.

Prevalence of microalbuminuria in this study was 11.25%. The mean urine microalbumin level was 37.95 ± 33.75 mg/day.

This study showed prevalence of elevated urine albumin creatinine ratio amounting to microalbuminuria in 11.25%. The mean urine albumin creatinine ratio was 36.78 ± 31.86 mg/gm.

This study showed overt proteinuria in 7.5% of HIV seropositive patients.

Microalbuminuria levels specifically correlated with CD4 counts. In this study 9 out of 9 patients with microalbuminuria were found to have CD4 counts ≤ 350/μL.

Present study revealed abnormalities of serum creatinine in 8 patients of which 7 patients were found to have CD4 counts ≤ 350/μL.

Present study recommends urinary screening for microalbuminuria in HIV patients to identify early renal involvement and minimize renal complications by early intervention.

CONCLUSION

- Microalbuminuria was significantly elevated in the study group, seen in 11.25% of cases. The mean urine microalbumin value was 37.95 mg/day.
- The prevalence of elevated urine albumin creatinine ratio amounting to microalbuminuria was 11.25% in the study group. The mean urine albumin creatinine ratio was 36.78 mg/gm.
- The microalbuminuria specifically correlated with CD4 counts, 9 out of 9 in the study group were found to have CD4 count ≤ 350/μL.
- Serum Creatinine levels were elevated in 8 patients, out of whom 7 were found to have CD4 count ≤ 350/μL.
- Overt proteinuria was present in 7.5% in the study group.
- Electrolyte abnormalities were not found in our study.

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PROFORMA

MICROALBUMINURIA IN HIV PATIENTS

NAME: **AGE:** **SEX:** **HOSPITAL NO:**

ADDRESS: **OCCUPATION:**

CD4 count **WHO STAGING:**

PRESENT COMPLAINTS:

LOSS OF APETITE

VOMITING

BREATHLESSNESS

FREQUENCY OF MICTURITION

OLIGURIA

LEG SWELLING

FACIAL PUFFINESS

HEMATURIA

ABDOMINAL PAIN

PAST ILLNESS

ATT INTAKE

DIABETES MELLITUS

HYPERTENSION

CORONARY ARTERY DISEASE

RENAL DISEASE

JAUNDICE

NSAID OR OTHER DRUG INTAKE

BLOOD TRANSFUSION

OTHERS (SPECIFY)

PERSONAL HISTORY

SMOKER

ALCOHOLIC

MARITAL STATUS

SEXUAL PROMISCUITY

IV DRUG ABUSE

GENERAL EXAMINATION:

HEIGHT : WEIGHT: BMI:

PULSE: BP:

ANAEMIA JAUNDICE CLUBBING

PEDAL EDEMA LYMPHADENOPATHY

SYSTEM EXAMINATION

CVS

RS

ABDOMEN

CNS

INVESTIGATION

HB% TC DC: P L E M B ESR

URINE: ALBUMIN SUGAR DEPOSITS

BLOOD: SUGAR UREA

SERUM: CREATININE ELECTROLYTES – Na+ K+

SERUM BILIRUBIN SGOT SGPT SAP

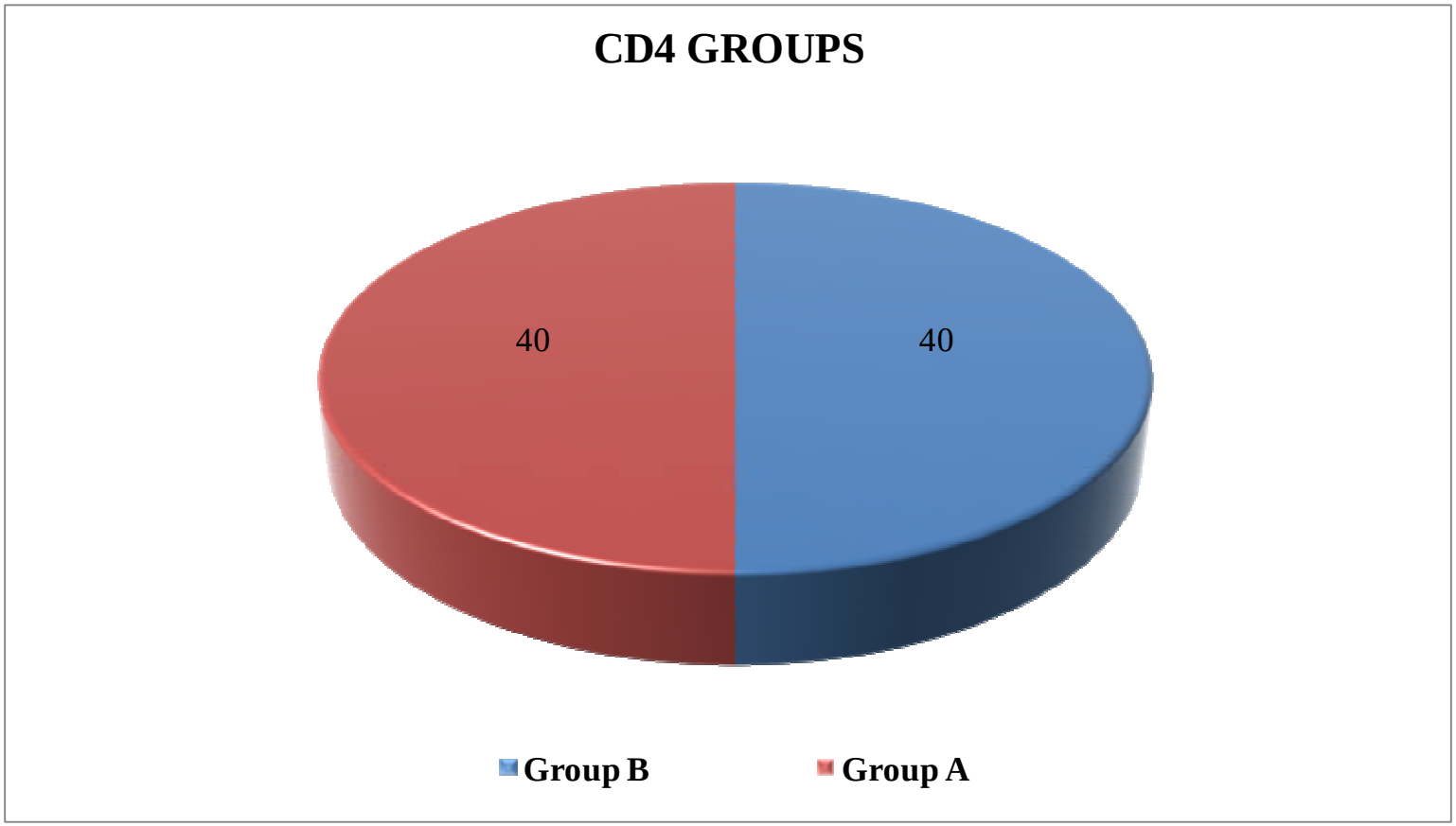
URINE: MICROALBUMIN

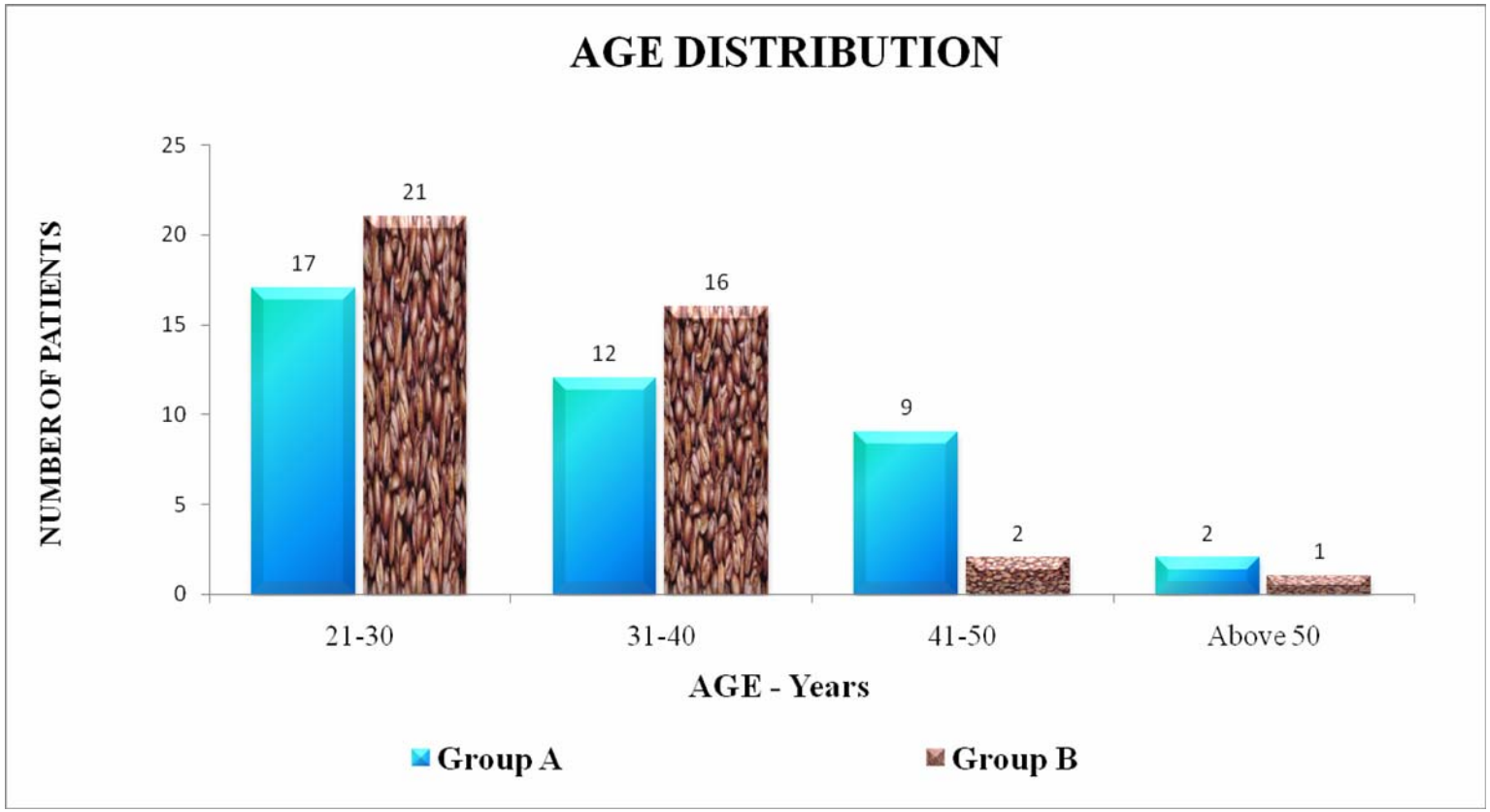
24 HRS URINE PROTEIN

ALBUMIN CREATININE RATIO

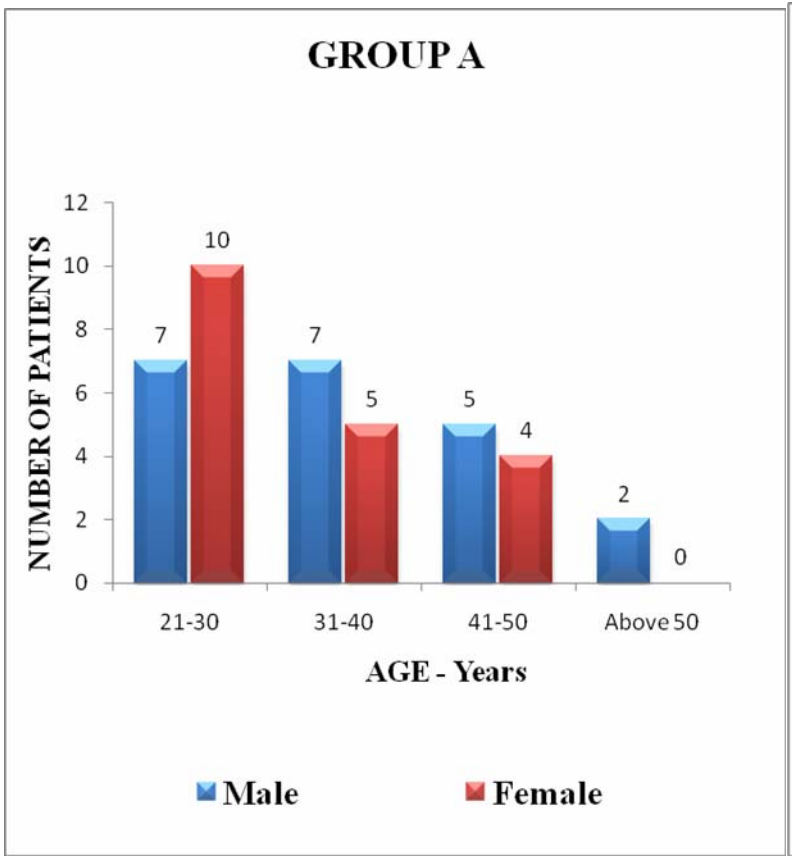
CHEST X-RAY ECG

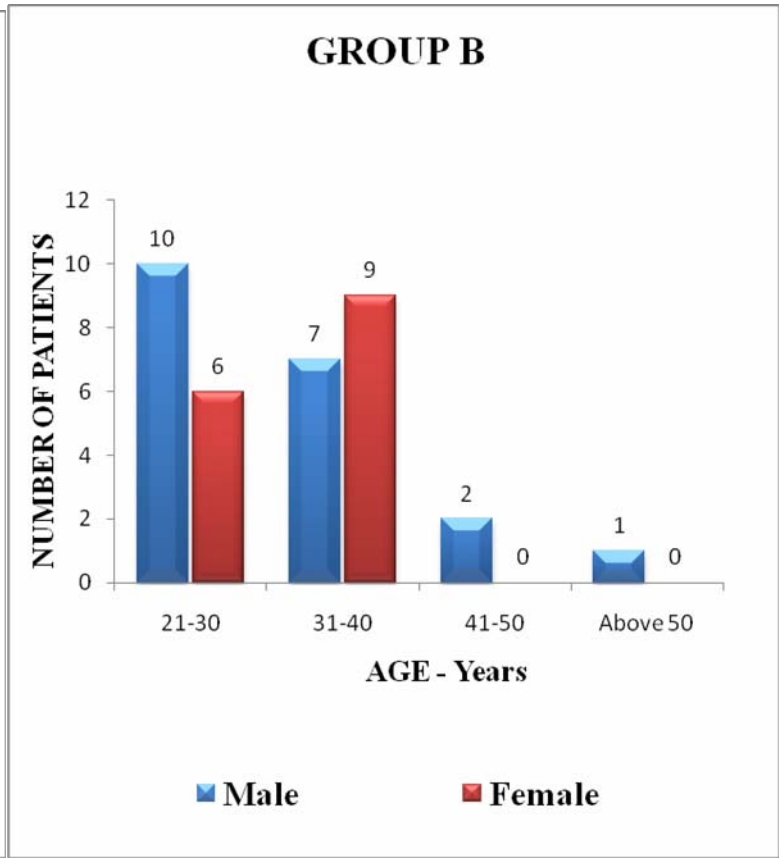
USG – ABD & KUB

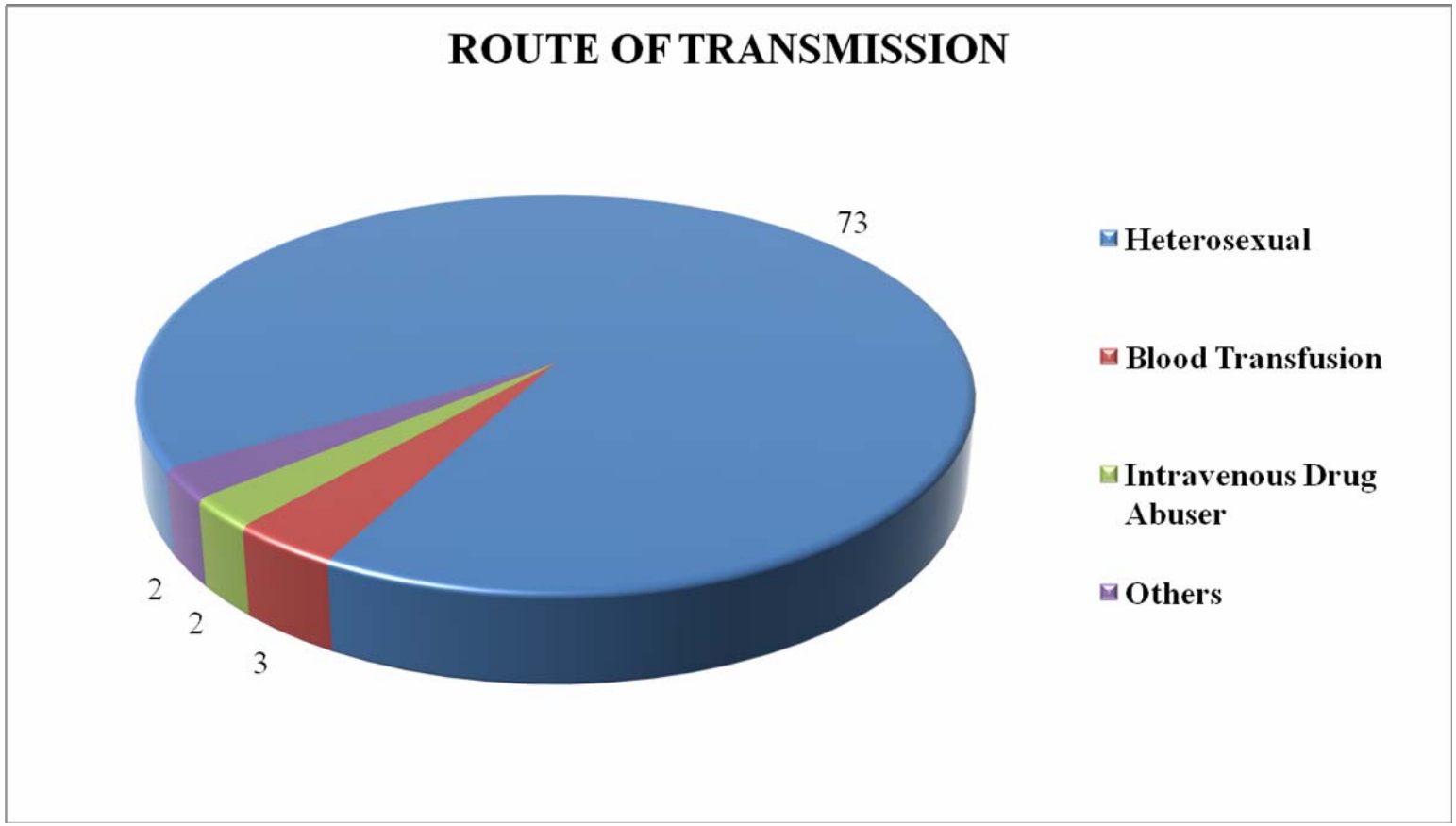

CD4 GROUPS
40
40
Group B
Group A

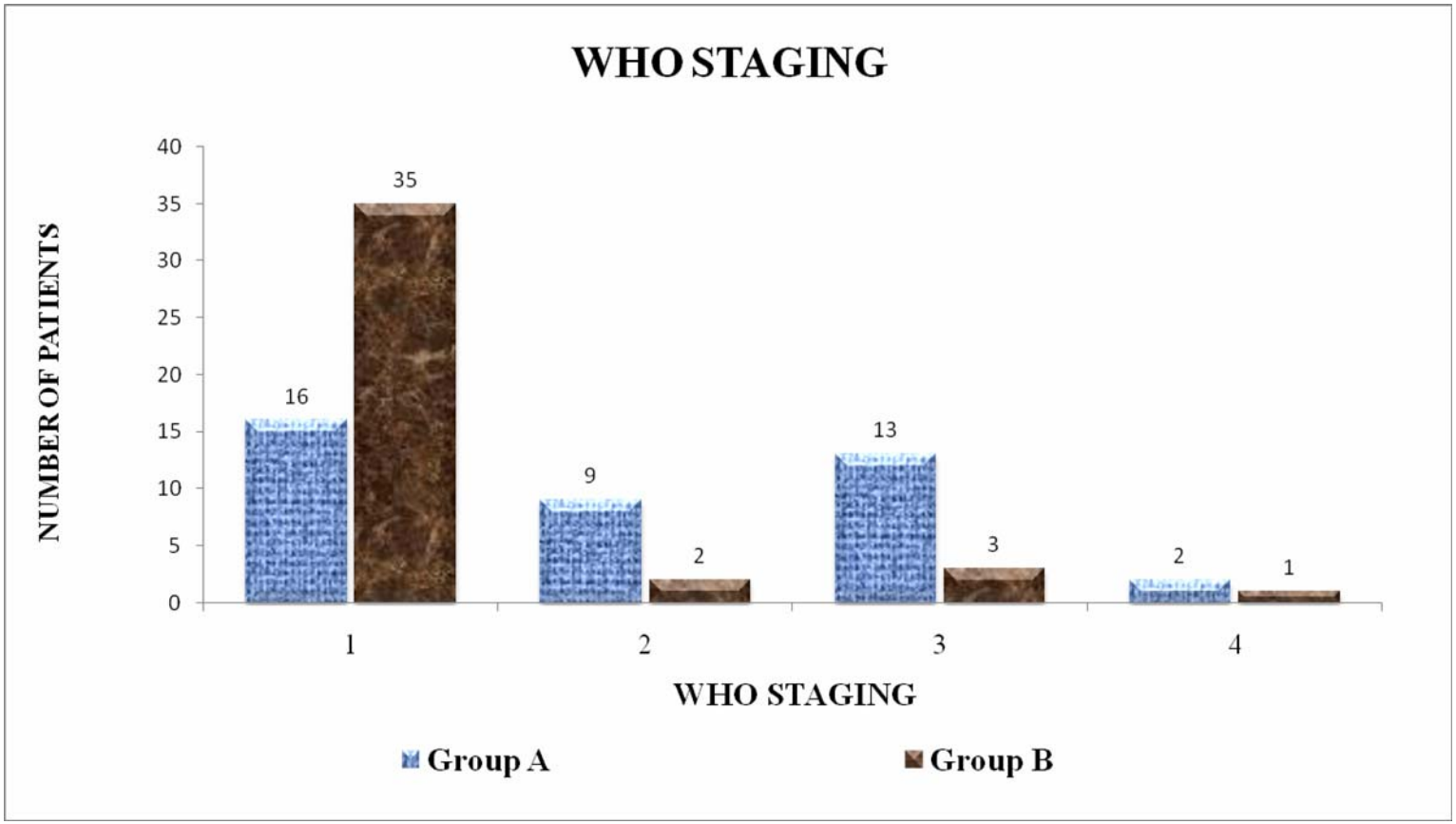

AGE DISTRIBUTION
NUMBER OF PATIENTS
25
20
15
10
5
0
17
21
12
16
9
2
2
1
21-30
31-40
41-50
Above 50
AGE - Years
Group A
Group B

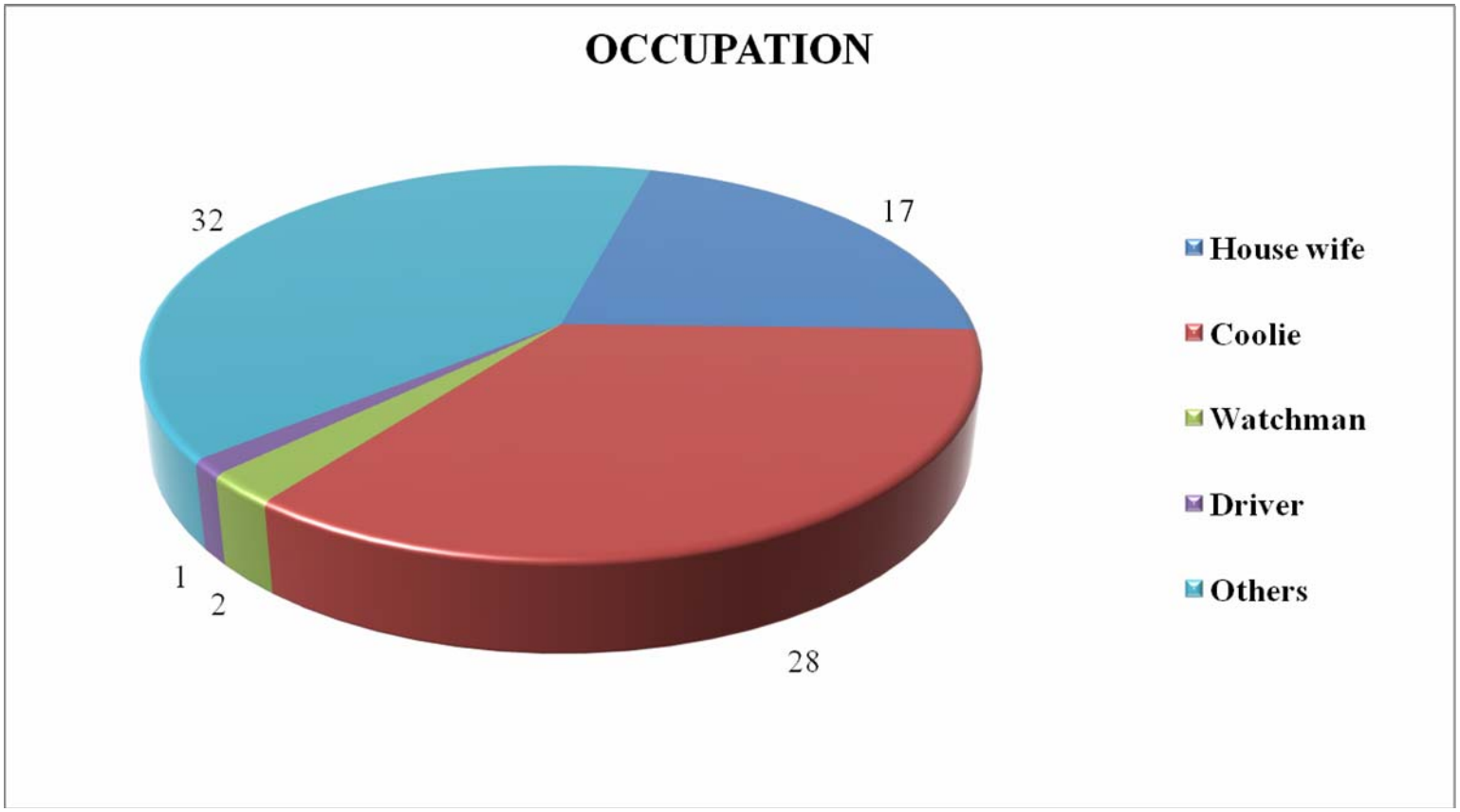
CD4 GROUP DISTRIBUTION IN RELATION TO AGE & SEX

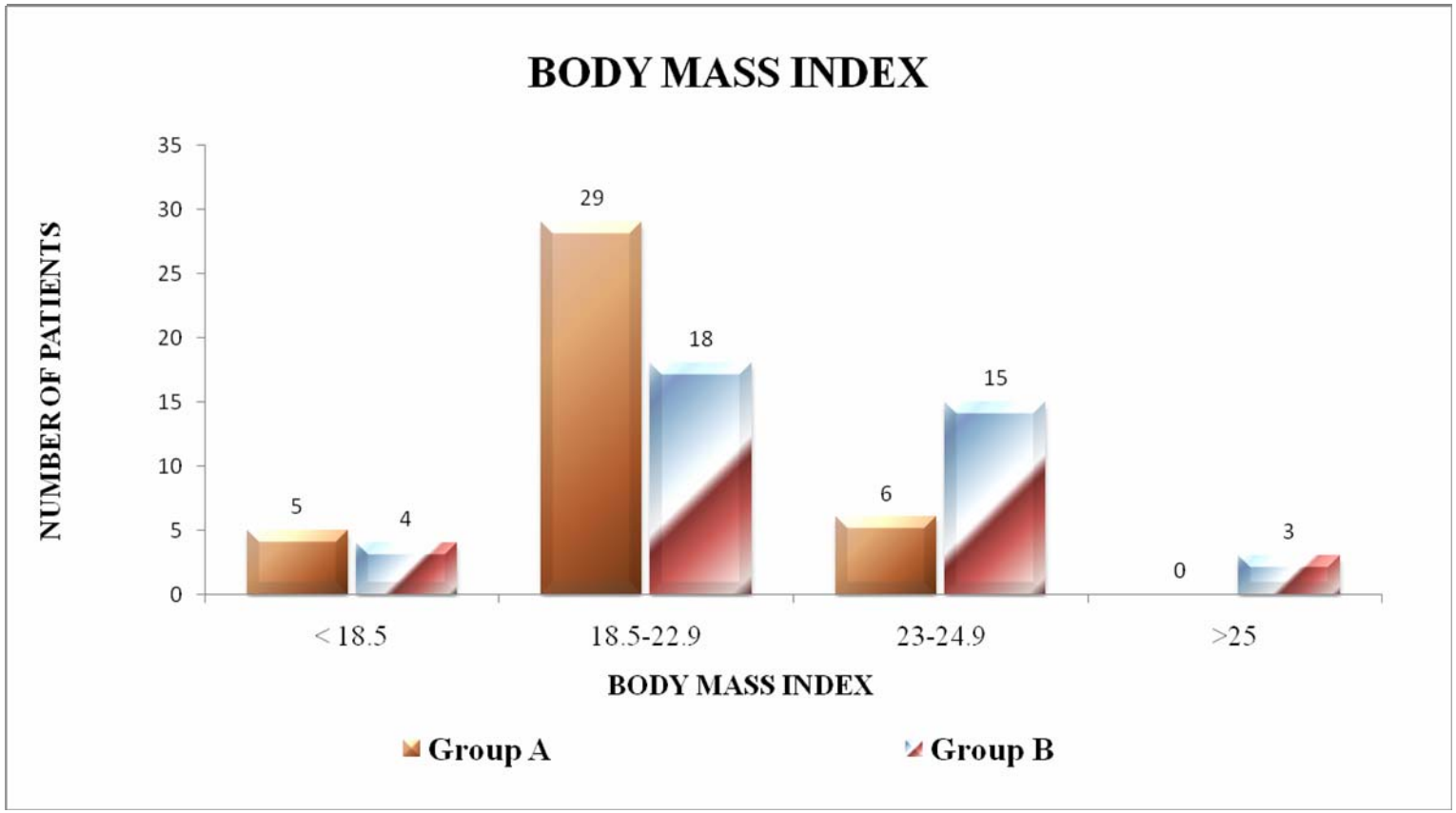





ROUTE OF TRANSMISSION
73
2
2
3
Heterosexual
Blood Transfusion
Intravenous Drug Abuser
Others


WHO STAGING
NUMBER OF PATIENTS
40
35
30
25
20
15
10
5
0
16
35
9
2
13
3
2
1
1
2
3
4
WHO STAGING
Group A
Group B


OCCUPATION
32
17
1
2
28
House wife
Coolie
Watchman
Driver
Others


BODY MASS INDEX
NUMBER OF PATIENTS
35
30
25
20
15
10
5
0
5
4
29
18
6
15
0
3
< 18.5
18.5-22.9
23-24.9
>25
BODY MASS INDEX
Group A
Group B

MICROALBUMINURIA DISTRIBUTION